INFLAMMATORY BIOMARKERS AND FUNCTIONAL BIOMECHANICS OF OLDER ADULTS WITH OSTEOARTHRITIS BEFORE AND AFTER TOTAL KNEE ARTHROPLASTY

by

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ABSTRACT

By the year 2030, there is expected to be a 6-fold increase in the number of annual total knee arthroplasty (TKA) surgeries. The growing demand for TKA has highlighted the need to develop improved measures for identifying modifiable factors that may be linked to poor physical performance and long-term outcomes following TKA. This body of work focuses on factors that may be linked to poor TKA outcomes, including the following: 1) physiological factors such as high sensitivity C-reactive protein (hs-CRP) and cytokines and 2) post-TKA functional outcomes that may be linked to future mobility deficits and risk of falling.

A total of 47 subjects with osteoarthritis (OA) scheduled for TKA, and 11 controls without OA were assessed in two separate clinical studies. Study #1 encompassed 31 TKA subjects stratified by hs-CRP: 15 with hs-CRP $\leq$1.0 mg/L and 16 with hs-CRP $\geq$4.0 mg/L. Study #2 included 16 subjects with OA scheduled for TKA and 11 controls without OA. In Study #1, synovial fluid (SF) and bone sections were sequestered during surgery; 12 cytokines were measured in SF and histological measures of inflammation were assessed in bone sections. Relationships between cytokines and hs-CRP were assessed. In Study #2, pre- and postoperative assessments of submaximal muscle force steadiness (MFS) and variability during gait and stair stepping were evaluated and compared to healthy controls.

Study #1 showed the presence of lymphocytes in 10 synovium and one bone sample (all from high hs-CRP group), and significant correlations between hs-CRP and cytokines interleukin (IL)-5 and IL-10. Study #2 showed that quadriceps MFS was significantly more impaired in the TKA subjects preoperatively, but not postoperatively compared to controls, and significantly improved between the pre- and postoperative visits. Additionally, there was a significant reduction in variability during gait between pre- and postoperative visits, but not during stair stepping.

The results suggest that inflammatory mechanisms contribute to OA progression, with hs-CRP being a possible predictive variable, combined with other comorbidities, of postoperative function. Further, postoperative functional measures such as MFS and variability during gait and stair stepping may provide rehabilitation targets for individuals following TKA that may predict future falls and declines in functional mobility.

This work is dedicated to my mother, Gay G. Smith, who passed away December 13, 2011, during my tenure as a PhD student. For her infinite wisdom to never place limitations on her daughters, I will always be grateful.

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CHAPTER 1

INTRODUCTION

Osteoarthritis (OA) is the most common type of arthritis, affecting nearly 43 million Americans (Elders, 2000; Dillon, 2006; Hootman et al., 2009). By the year 2030, this number is expected to reach 72 million or nearly 25% of the adult U.S. population (Elders, 2000). The combined annual cost of medical care and lost wages due to OA is expected to approach $100 billion by the year 2020 (Elders, 2000). This growing financial burden combined with the negative impact OA has on quality of life has resulted in heightened interest in not only developing more objective measures for identifying OA early in the disease process, but also improving physical function following knee replacement surgery (Malemud and Goldberg, 1999; Fernandes et al., 2002).

The symptoms associated with OA are generally well known and include pain and loss of motion, resulting in restricted activity, decreased neuromuscular control, impaired proprioceptive acuity, and loss of independence during activities of daily living (Crepaldi and Punzi, 2003; Punzi and Oliviero, 2005). One of the most common treatment modalities for late stages of OA is the total knee arthroplasty (TKA) surgical procedure. TKA is an invasive surgery that is typically performed when all other treatment options

have been exhausted, with the deciding factor to undergo surgery being highly variable between individuals (Ackerman et al., 2009).

While TKA is typically effective for pain relief, it often falls short in achieving similar improvement in both physical and muscle function outcomes (Mizner and Snyder-Mackler, 2005; Meier et al., 2008; Petterson et al., 2008). Despite long-term muscle and mobility deficits, the demand for the pain-reducing TKA procedure continues to grow, with an expected 6-fold increase by the year 2030 (Hootman et al., 2009), as does the need to identify modifiable factors that may be linked to suboptimal physical function following surgery (Startzell et al., 2000; Scott, 2005). The research described herein explores select physiological factors linked to the progression of OA and sub-optimal TKA outcomes, as well as modifiable physical and muscle function parameters that may lead to improved early interventions, as well as more effective postoperative rehabilitation strategies.

1.1 Inflammatory Biomarkers and Osteoarthritis

To better understand physiological factors that may correspond with poor surgical outcomes, recent research has focused on elevated inflammatory biomarkers such as C-reactive protein (CRP) and cytokines such as interleukin (IL)-6, IL-10, IL-5, and tumor necrosis factor alpha (TNF- α) as possible contributing factors. CRP, in particular, is synthesized in the liver in response to inflammation, infection, and injury and has been independently correlated with lower limb strength and risk of fracture in elderly adults and in individuals with OA (Cauley et al., 2007; Hamer and Molloy, 2009; Levinger et al., 2011). Delineating the correlation between CRP and various inflammatory disease

processes such as OA was made possible by the development of a high-sensitivity laboratory testing method for measuring CRP (i.e., hs-CRP). The ability to measure CRP with greater precision has enabled researchers to stratify individuals' risk of complications and severity of various chronic inflammatory disease processes based on hs-CRP levels (Pearson et al., 2003). Hs-CRP has also been correlated with symptoms of pain and stiffness in individuals with OA, but the relation to long-term functional outcomes in TKA patients has not been investigated (Sturmer et al., 2004). Similarly, cytokines are small, immunomodulating protein molecules that are produced throughout the body, with concentrations that may increase up to 1000-fold in response to trauma or infection. Several cytokines are induced by oxidative stress, suggesting a significant role in chronic inflammation (Vlahopoulos et al., 1999; Felson et al., 2007).

Synovial fluid (SF) cytokine levels have been shown to correlate with OA disease activity and levels of hs-CRP, and more specifically, inflammatory cytokines such as IL-6 and IL-8 have been shown to upregulate expression of hs-CRP (Gabay and Kusher, 1999). For example, Bertazzolo et al. (1994) showed a relationship between SF IL-6 and IL-8 and indices of inflammation such as white blood cells and total protein, whereas others reported evidence of a major role of IL-1β, IL-6, and IL-8 in the pathogenesis of joint diseases, including OA (Bertazzolo et al., 1994; Westacott and Sharif, 1996; Punzi et al., 2002). Levinger et al. also showed a relationship between markers of inflammation in muscle tissue and reduced strength in patients with knee OA (Levinger et al., 2011).

The ability to predict long-term TKA surgical success based on clinical laboratory biomarkers has broad implications. While the current body of literature includes important information regarding the relation between biomarkers of inflammation and

OA, further research is warranted to investigate the potential cross correlations between inflammatory markers such as hs-CRP and cytokines, as well as functional parameters related to activities of daily living and long-term outcomes in TKA patients.

1.2 Postoperative Functional Outcomes and Relation to Chronic Inflammation

Postoperative functional outcomes following TKA can take many forms from quality of life assessments and range of motion, to lower extremity strength and steadiness, as well as the ability to perform activities of daily living such as walking and stair stepping. Correlations between chronic inflammation, as measured by hs-CRP and SF cytokine levels, as well as relationships between hs-CRP and clinical outcomes may have implications for predicting risk factors for poor outcomes postoperatively.
To better understand these relationships, an investigation of how TKA influences functional parameters such as quadriceps strength, lower extremity force control, and the ability to navigate stairs, as well as their relationship to measures of chronic inflammation such as hs-CRP is warranted. The basis for these efforts lies in the fact that the process of arthritis results in disruption of the normal neuromuscular mechanisms necessary for normal activation and control of muscle force production (Topolski et al., 2006). This disruption occurs early in the disease cycle, and there is evidence that chronic inflammation plays a significant role in disease progression and disruption of this process.

A significant component of this disruption is quadriceps arthrogenic muscle inhibition (AMI), or the inability to fully activate the quadriceps muscle. Quadriceps

AMI is associated with changes in the discharge of afferent, articular sensory receptors resulting from swelling, inflammation, joint laxity, and damage to knee joint afferents, all of which are common manifestations of OA (Rice and McNair, 2010). Swelling, in particular, has been shown to independently alter joint afferent discharge by increasing the firing frequency and recruitment of group II afferents (Wood and Ferrell, 1984; Ferrell et al., 1986; Ferrell, 1987). This finding is explained by the positive correlation between joint effusion and intra-articular pressure (IAP), wherein greater effusion correlates with higher IAP, with the greatest effects at the extremes of motion (Schaible and Schmidt, 1983; Jones et al., 1987; Dorn et al., 1991; Jensen and Graf, 1993). Not surprisingly, in the presence of swelling, the extremes of motion correspond with the greatest muscle inhibition, where IAP and afferent discharge are the highest (Stratford, 1982; Krebs et al., 1983; Shakespeare and Rigby, 1983; Jones et al., 1987; Jensen and Graf, 1993; Reeves and Maffulli, 2008).

Similarly, inflammatory responses and joint laxity also contribute to quadriceps AMI by increasing joint afferent discharge, inflammation via sensitization of free nerve endings innervated by group III and IV afferents (Coggeshall et al., 1983; Schaible and Schmidt, 1988; Schepelmann et al., 1992), and joint laxity via increases in the activation of mechanoreceptors and nociceptors (Hurley et al., 1997; Rice and McNair, 2010). While both of these effects result in greater AMI due to nociceptive influences, the relationship between AMI and pain is inconsistent (Rice and McNair, 2010) in patients with OA (Fitzgerald et al., 2004) as well as following TKA (Stevens et al., 2003; Mizner et al., 2005). Indeed, research shows that while the presence of pain may accompany AMI, inhibition occurs in the absence of pain as well.

Although the consequences of OA discussed thus far result in increases to joint afferent discharge, it is important to note that these disruptions may be accompanied by simultaneous decreases in afferent output due to damage to articular receptors (Johansson, 1991; Young, 1993; Hurley et al., 1997; Konishi et al., 2002) and subsequent influences to reflex pathways within the spinal cord. The potential contributors include group I nonreciprocal (Ib) inhibitors (Iles et al., 1990), interneurons associated with the flexion reflex (Lundberg et al., 1987; Leroux et al., 1995; McCrea, 1996), as well as dysfunction of the gamma (γ)−loop (Rice and McNair, 2010), with the overall effect being inhibition of the quadriceps α-motoneuron pool (Ferrell et al., 1988; Young, 1993; Hurley et al., 1997; Konishi et al., 2002). Research suggests that all three spinal reflex pathways contribute to AMI, with the relative contributions dependent on factors such as the extent and location of joint damage, swelling, inflammation, and laxity.

In individuals with OA, the different neural mechanisms described above involve a series of complex innervation strategies that have the net result of contributing to quadriceps AMI and associated force control. TKA, by nature, results in explicit disruption of the joint capsule and ligamentous structures, as well as alterations to joint motion and, therefore, would be expected to influence mechanisms that contribute to AMI that rely specifically on afferent discharge from these structures. Although TKA has been shown to reverse some of these impairments by improving proprioception and joint stability, similar improvements in muscle and mobility deficits following TKA are often not realized. Thus, the significance of these neuromuscular changes in individuals that undergo TKA is not well understood. That is, the factors that influence the extent to which these changes affect functional outcomes following TKA have not been clarified,

nor is it apparent whether these changes are greater in individuals exhibiting evidence of chronic inflammation (i.e., higher hs-CRP levels). Fig. 1.1 is a schematic that describes the interactions between lifestyle, osteoarthritis, inflammatory biomarkers, and proprioceptive and neuromuscular changes.

1.3 Relationship between Functional Deficits and Long-Term TKA Outcomes

As discussed in the previous sections, individuals who have undergone TKA continue to have significant muscle and mobility deficits related to impaired quadriceps function, despite resolution of their knee pain (Mizner RL, 2005; Meier et al., 2008; Petterson et al., 2008). In particular, individuals with TKA have been shown to have deficits in quadriceps force production, as well as impaired ability during stair stepping tasks compared to healthy controls (Andriacchi et al., 1982; Andriacchi et al., 1997). Considering the muscle and mobility deficits following TKA, this finding is not unexpected, especially since stair stepping is one of the most demanding daily activities controlled by the quadriceps muscle, and not surprisingly, one of the highest risk activities associated with falling (Kuster et al., 1997; Startzell et al., 2000; Scott, 2005).

In fact, falls are a major disability risk factor for individuals with knee OA, and for those aged 65 and older, falls are the leading cause of accidental injury and death, as well as long-term disability (Startzell et al., 2000; Scott, 2005). Based on a recent study, 24% of knee OA patients fell during the 3 months prior to TKA surgery, and half of these (~12%) fell within the first postoperative year (Andriacchi et al., 1982). Given the anticipated increase in TKA surgeries over the next two decades, this equates to over

350,000 falls within the first postoperative year, with nearly 30% expected to result in significant disability (Schiller et al., 2007). Additionally, older individuals with knee OA who have a preoperative history of falling are still nearly eight times as likely to continue to fall after TKA surgery compared to a similar cohort of nonfallers who receive TKA (Swinkels et al., 2009).

While the prevalence of disability associated with falls in elderly individuals is well-established in the literature (Schiller et al., 2007), the effect of TKA on muscle and functional parameters that may predispose an individual to fall remain undefined. In other words, we do not have an algorithm to predict whether someone is susceptible to falling or long-term disability after TKA surgery. What has been established, however, is that a large cohort of TKA recipients remains at high risk of falling, characterized by impaired muscle strength and movement patterns following TKA surgery, even after adjustments for age and co-morbid conditions (Swinkels et al., 2009). Accordingly, there is substantial support for research aimed at better understanding the factors that contribute to the likelihood of long-term disability following TKA surgery.

The ability to control lower extremity submaximal muscle forces, in particular, has been shown to be an independent risk factor for age-related impairment of physical performance, such as increased tendency to fall. More specifically, quadriceps muscle force steadiness (MFS), which assesses the ability to maintain constant submaximal muscle forces, has been positively correlated with performance during stair stepping in patients with hip OA (Pua et al., 2010). While the relationship between MFS has not been investigated in patients before and after TKA, there is evidence that those with knee OA have impaired MFS when compared to healthy controls (Hortobagyi et al., 2004).

Variability during gait is another parameter that has been shown to predict long-term risk of falling and mobility deficits in different populations. However, there is a relative lack of data on how these parameters are affected by TKA and whether they can be used to predict long-term functional outcomes.

Gait is a multifaceted and complex task that requires coordinated movement between both central and peripheral neuromuscular control mechanisms. While there is a growing body of evidence to suggest that gait parameters can be used to predict long-term risk of falling and mobility deficits in different populations, there is very little data on how these parameters are affected by TKA and whether they can be used to predict long-term functional outcomes.

Knee OA contributes to quadriceps weakness, inhibition, and associated dysfunction, as well as impaired neural control and proprioception (Swanik et al., 2000; Knoop et al., 2011; Montero-Odasso et al., 2011), which have been suggested to contribute to altered spatio-temporal, kinematic, and kinetic gait patterns compared to healthy controls (Collopy et al., 1977; Marks and Quinney, 1993; Lafuente et al., 2000; Suter and Herzog, 2000; Brach et al., 2008; Astephen Wilson et al., 2011). As a result of these deficits, knee OA is associated with a distinctive gait pattern, which includes slower gait speed and cadence, reduced stride length, and altered kinematics and kinetics during the loading phase of the gait cycle (Lafuente et al., 2000; Suter and Herzog, 2000; Brach et al., 2008). More recently, researchers have identified stance time variability (STV) as a particularly important measure as it has been shown to be highly correlated with fall risk and central nervous system (CNS) impairment in older adults, even after consideration for gait speed (Marks and Quinney, 1993; Kinoshita and Francis, 1996; Maki, 1997;

Brach et al., 2008). Other measures of gait variability have also been correlated with severity of OA (Astephen Wilson et al., 2011), as well as risk of future falls and gait instability before and after TKA (Collopy et al., 1977; Hatfield et al., 2011).

Since falls occurring on stairs are common, and falls during stair descent outnumber falls during stair ascent (Startzell et al., 2000; Scott, 2005), a characterization of variability during stair stepping is warranted. Variability during stair stepping, similar to variability during level walking, may provide an important rehabilitation target for individuals following TKA, as well as provide another parameter that may predict future falls and declines in functional mobility.

To our knowledge, there are no peer-reviewed published studies that have investigated MFS parameters from a functional perspective in individuals who have undergone TKA surgery. Additionally, variability in gait parameters has not been correlated with deficits during other functional tasks, such as stair stepping, before and after TKA. Accordingly, the specific aims of the clinical studies that encompass the entirety of the research presented herein are presented below.

1.4 Specific Aims

The specific aims of the research described herein are as follows:

1) To investigate the relationship between serum hs-CRP and synovial fluid cytokines, and postoperative functional outcomes in patients with OA who elected to undergo TKA.

2) To compare MFS of submaximal quadriceps force output in individuals with knee OA before and after TKA, and to a group of age-matched controls with native knees.

3) To investigate gait variability, as assessed by STV, during level walking and stair ascent and descent in older adults with OA before and at 6 months after TKA, and compare to an age- and sex-matched group of healthy controls with native knees; and evaluate the relationship of STV between level walking and stair ascent and descent.

1.5 Hypotheses

Based on the specific aims described above, it was hypothesized that:

1) Hs-CRP would correlate with indices of inflammation found in bone and synovium biopsies, as well as with postsurgical functional improvement, in patients undergoing TKA.
2) Preoperatively, the surgical leg would exhibit impaired MFS compared to the control group, and because the effects of TKA surgery on MFS are unknown, we proposed the null hypothesis that at 6 months following surgery, MFS would not significantly improve on the surgical leg compared to their preoperative study visit, or the control group.
3) Preoperatively, the surgical leg would exhibit significantly greater STV during both level walking and stair ascent and descent than at 6 months postoperatively; preoperatively, the surgical leg would exhibit greater STV during level walking and stair ascent and descent than a group of healthy controls with native knees; postoperatively, the surgical leg would exhibit similar STV during level walking and stair stepping as a group of healthy controls; and there would be a significant positive correlation in the TKA-GROUP between STV during level walking and

STV during stair ascent and stair descent at both the pre- and postoperative study visits.

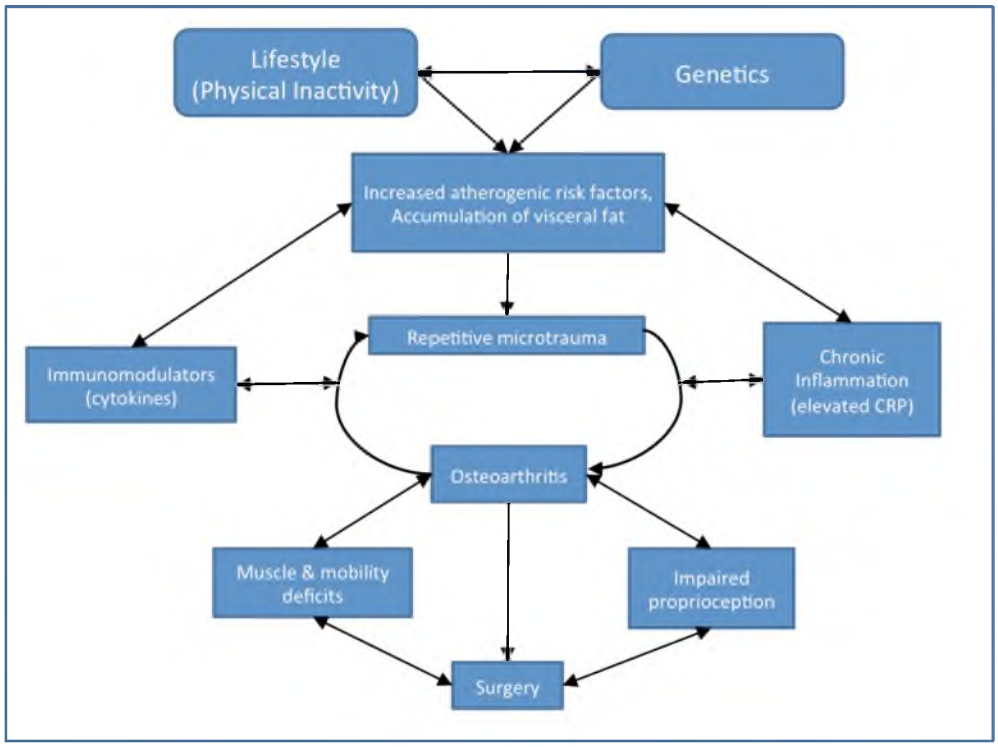

Fig. 1.1. Interactions between lifestyle and OA progression

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CHAPTER 2

SIGNIFICANCE OF C-REACTIVE PROTEIN IN OSTEOARTHRITIS AND TOTAL KNEE ARTHROPLASTY

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Significance of C-reactive protein in osteoarthritis and total knee arthroplasty outcomes

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Abstract:

Background: The relationship between systemic inflammatory processes to total knee arthroplasty (TKA) outcomes remains unclear. This study investigates the relationship between serum high-sensitivity C-reactive protein (hs-CRP) and functional outcomes post-TKA.

Methods: A total of 31 patients with osteoarthritis (OA) who underwent TKA were enrolled in the study; 15 with hs-CRP ≤1.0 mg/l (low hs-CRP group) and 16 subjects with hs-CRP ≥4.0 mg/l (high hs-CRP group). During surgery, synovium and bone sections were sequestered, formalin-fixed, and paraffin embedded for slide preparation. Tissue sections were stained with hematoxylin and eosin and analyzed using a light microscope. A total of 12 cytokines were measured in synovial fluid samples from the knee joint at time of surgery and analyzed using the Luminex Multi-Analyte Profiling System. Relationships between cytokines and hs-CRP were assessed using Spearman correlation coefficients. Student's *t*-tests were used to compare Short Form health outcomes survey (SF-12) health outcomes between high and low hs-CRP, and presurgical and postsurgical visits.

Results: Mean ± standard deviation (SD) baseline and 1-year hs-CRP values for the low hs-CRP group were 0.55 ± 0.23 mg/l and 1.22 ± 1.32 mg/l, respectively ($n = 15$; $p = 0.051$) and for the high hs-CRP group were 7.86 ± 5.98 mg/l and 14.11 ± 38.9 mg/l, respectively ($n = 13$; $p = 0.54$). Lymphocytes were present in 10 synovium and one bone sample (all but one from high hs-CRP group). Interleukin (IL)-5 and IL-10 were significantly correlated with hs-CRP ($p = 0.0137$ and $p = 0.0029$, respectively). The low hs-CRP group exhibited significant improvement in the physical component of SF-12 at 6 and 12 months compared with baseline, whereas the high hs-CRP group exhibited significant improvement only at 6 months. Body mass index (BMI) had a significant positive correlation with presurgical hs-CRP.

Conclusions: The results of this study provide support for inflammatory mechanisms contributing to the OA progression, with hs-CRP being a possible predictive variable, combined with BMI and other comorbidities, of post-TKA function.

Keywords: Osteoarthritis, inflammation, C-reactive protein, total knee arthroplasty

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Introduction

Osteoarthritis (OA) is the most common type of arthritis, affecting nearly 27 million Americans [Lawrence *et al.* 2008], or 12% of adults in the United States. By the year 2030, this number is expected to reach 72 million or about 20% of the adult US population [Bitton, 2009; Elders, 2000]. The combined annual cost of medical care and lost wages due to OA is expected to approach US$100 billion by the year 2020 [Bitton, 2009; Elders, 2000; Leigh *et al.* 2001]. This growing financial burden combined with the negative impact OA has on quality of life has resulted in heightened interest in developing

more objective measures for identifying OA early in the disease process, as well as improved treatment modalities and rehabilitation protocols.

OA is characterized by joint space deterioration, pain, and loss of motion resulting in restricted activity and loss of independence during activities of daily living [Crepaldi and Punzi, 2003; Punzi and Oliviero, 2005]. The typical treatment modalities for OA include drug therapy, exercise, weight control, and in more severe cases, surgical intervention including total knee arthroplasty (TKA). While the goals of TKA are relief of pain and improvement in function, the factors that influence long-term surgical treatment outcomes of OA have not been clearly delineated [National Institutes of Health, 2003].

Bone quality has been implicated in the success rate of primary surgical outcomes as well as revisions, and has been the focus of recent research to identify the clinical relevance of biomarkers of inflammation including high-sensitivity C-reactive protein (hs-CRP) [Conrozier *et al.* 1998] and cytokine levels [Perovic-Rackov and Pejnovic, 2006] in relation to disease activity and bone quality.

CRP, in particular, is produced in response to inflammation, infection, and injury, and has been correlated with complications related to conditions such as hypertension, cardiovascular disease, and diabetes [Ablij and Meinders, 2002; Dalton *et al.* 2003; DiNapoli and Papa, 2003; Gabay and Kusher, 1999]. In relation to OA, elevated levels of CRP have been correlated with synovial fluid interleukin (IL)-6 and degree of synovial fluid infiltration [Pearle *et al.* 2007], as well as symptoms of pain and stiffness, radiographic gradings [Sturmer *et al.* 2004; Takahashi *et al.* 2004], and disease progression [Conrozier *et al.* 1998, 2000; Sharif *et al.* 2000]. However, the relation between hs-CRP and localized cytokine levels, as well as surgical outcomes is still unclear.

The purpose of this study was to investigate the relationship between serum hs-CRP and postoperative functional outcomes in patients with OA who elected to undergo TKA. It was expected that hs-CRP would correlate with indices of inflammation found in bone and synovium biopsies, as well as with postsurgical functional improvement, in patients undergoing TKA.

Methods

The study was approved by an Institutional Review Board and all patients consented prior to enrollment in the study. Serum hs-CRP and synovial fluid cytokine measurements were obtained in 31 subjects, between 2007 and 2009, who underwent either unilateral or bilateral TKA, all of which were performed by the same orthopedic surgeon (Park City, UT). Subjects were enrolled based on the diagnosis of OA, which was confirmed preoperatively with radiographs and careful review of past medical conditions. Additional examination of the patients' extremities was performed to exclude patients who had any typical signs/deformities of rheumatologic disease. None of the patients in the study had a previous history of rheumatoid arthritis (RA) or exhibited signs/symptoms of RA. Patients were enrolled based on their hs-CRP: 15 were enrolled with an hs-CRP level less than or equal to 1.0 mg/l (low hs-CRP group) and 16 with an hs-CRP level greater than or equal to 4.0 mg/l (high CRP group). Owing to the lack of hs-CRP risk stratification levels for OA patients, subjects were stratified into hs-CRP levels based on levels associated with low and high risk of developing stroke, myocardial infarction, and severe peripheral vascular disease [Myers *et al.* 2009].

Serum hs-CRP was measured prior to surgery and at 1-year postsurgery using the ARCHITECT c8000 (Abbott Diagnostics, Abbott Park, IL), which is an open-reagent system that utilizes spectrophotometry to analyze samples. Subjects included males or females between 45 and 76 years of age who were not using medication that may artificially alter hs-CRP including lipid-lowering therapies such as HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors, fibric acid derivatives, niacin, or bile acid sequestrants within 6 weeks of study enrollment. Other exclusion criteria included: (a) current use of oral hormone replacement therapy (HRT); (b) current treatment with cyclosporin, tacrolimus, azathioprine, or other immunosuppressants including chronic use of oral glucocorticoids; (c) current use of insulin and/or an oral hypoglycemic agent; (d) history of malignancy within the past 5 years, with the exception of basal cell or squamous cell carcinoma of the skin; (e) use of thyroid replacement therapy that was initiated or modified within the last 3 months; (f) presence of a known chronic inflammatory condition not related to bone health such as, but not limited to, severe lupus or inflammatory

bowel disease; (g) history of alcohol or drug abuse within the past 1 year; and (g) participation in another investigational drug study <30 days before enrollment in the current study.

Gross bone appearance (bone health) was evaluated during surgery using a five-point qualitative scale. The bone health score was based on the surgeon's qualitative assessment of bone color, density, and visual presence of cysts and/or necrosis where a score of '1' represented poor bone health and '5' represented good bone health, with the following scale (1 = presence of cystic/necrotic disease; 2 = average density, grayish/pale color, and precystic/oxidative disease; 3 = moderate density and minimal oxidative changes; 4 = moderate to optimal density and golden color, and slight to no signs of inflammation; and 5 = optimal density, golden color, and no inflammation). Evaluations were performed independent of knowledge of hs-CRP levels and were confirmed by the physician's assistant also participating in the surgery.

During surgery, synovium and bone sections removed from the femoral condyle to perform the TKA were sequestered, formalin-fixed, and paraffin embedded for slide preparation. Tissue sections were stained with hematoxylin and eosin (H&E) and analyzed using a light microscope by a trained pathologist (ARUP Laboratories, Salt Lake City, UT). Results were compared to identify correlations between presence or absence of inflammatory cells and hs-CRP values.

A small sample of synovial fluid was removed from around the knee joint during surgery and analyzed by ARUP Laboratories (Salt Lake City, UT) for cytokine concentrations. For subjects with bilateral knee replacements, one sample was obtained from each knee. A total of 12 cytokines were measured using the Luminex Multi-Analyte Profiling System, developed at ARUP Laboratories (Salt Lake City, UT); IL-1b, IL-2r, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, tumor necrosis factor (TNF)-α, CD401, and interferon (IFN)-γ. The multiplexed cytokine assay was developed and validated in the ARUP Institute for Clinical and Experimental Pathology using a standard sandwich capture format and has been described previously [Martins *et al.* 2002, 2004].

Radiograph reviews were performed to identify correlations in rehabilitation and progression of healing between the low and high hs-CRP groups. Evaluations were performed using the Knee Society Roentgenographic Scoring System (KRSS) [Ewald, 1989], a standardized scoring system that allows comparisons across implant types and institutions. Based on the KRSS, a seven zone femoral implant component, seven zone tibial implant component, and five zone patellar implant component were used for the purposes of scoring. The scoring system for each of the three components is determined by measuring the width of the radiolucent lines for each of the zones (in millimeters). The total widths are added together for each zone and each of the three components. For each subject, lucency was measured at all implant component zones on the 6 week (Study Visit 3), 6 month (Study Visit 4), and 1 year (Study Visit 5) radiographs. A total score of 4 or less in any zone was considered insignificant, 5–9 indicated that the patient should be closely followed for progression, and 10 or greater signified possible or impending failure regardless of symptoms. In the event that migration or shifting of the prosthesis was present on the radiograph, this was considered as a possible or impending failure regardless of the total score [Ewald, 1989].

Health outcomes were assessed using the SF-12v2 Health Survey which was completed at baseline (preop), 6 months postop, and at 12 months postop using categorical, norm-based scoring for physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). Physical component summary (PCS) and mental component summary (MCS) values were also computed. Raw scores were converted to norm-based scoring using methods described in the SF-12v2 User's Manual. PCS and MCS scores were also converted to z-scores and then transformed using coefficients presented in the SF-12 User's Manual [Ware *et al.* 2002].

Statistical analyses

Subject demographics were summarized using descriptive statistics. Tests for equal variance were performed and appropriate two-tailed Student's t-tests were used to compare bone scores, body mass index (BMI), and age between low and high hs-CRP groups. Two-tailed t-tests were also used to compare SF-12 results between high and low hs-CRP, and two-tailed t-tests for paired data were used to compare results between presurgical and postsurgical visits. Missing data

were excluded analysis by analysis, allowing for different sample sizes across tests.

Qualitative relationships were evaluated between presurgical serum hs-CRP and bone and synovium histological assessments. Histological assessments were performed by a trained pathologist at ARUP laboratories.

For subjects who had more than one synovial fluid sample (i.e. five subjects who had bilateral TKA and five subjects who had unilateral TKA, but had more than one tissue sample sequestered from the same knee), the variability within samples was compared with the variability between subjects. The correlation within subjects for all samples was greater than between subjects and, therefore, the samples within subjects were averaged and this value was used for comparison between subjects.

Multiple variable logistic regression analyses were performed to identify correlations between low and high hs-CRP and synovial fluid cytokines. Cytokine results were determined to have a non-normal distribution and, therefore, spearman correlation coefficients were used and receiver operating characteristic (ROC) curves were developed to evaluate sensitivity *versus* specificity of hs-CRP compared with cytokines, and area under the curve (AUC) for each variable compared with hs-CRP.

Results

A total of 31 subjects were enrolled in the study with one subject in the high hs-CRP group discontinuing after Study Visit 2 due to non-compliance with Study Visits 3–5. This subject underwent TKA, and synovium and bone samples were sequestered during surgery and, therefore, these data were included in the cytokine and histological analyses, but not in the SF-12 analyses. Two additional subjects in the high hs-CRP group did not complete the 1-year hs-CRP measurement.

Five subjects underwent bilateral TKA; three in the low hs-CRP group and two in the high hs-CRP group. A total of 28 subjects were implanted with a Duracon press fit implant (Stryker Orthopaedics, Mahwah, NJ), and three subjects were implanted with the Triathlon press fit implant (Stryker Orthopaedics, Mahwah, NJ). Patient demographics are summarized in Table 1.

hs-CRP

Baseline hs-CRP values ranged from 0.3 to 1.0 mg/l (mean ± SD: 0.55 ± 0.23 mg/l; $n = 15$) for the low hs-CRP group and from 4.4 to 27.2 mg/l (mean ± SD: 7.86 ± 5.98 mg/l; $n = 16$) for the high hs-CRP group. The mean ± SD, 1-year follow-up hs-CRP for the low and high CRP groups were 1.22 ± 1.32 mg/l ($n = 15$) and 14.11 ± 38.9 mg/l ($n = 13$), respectively. There was no 1-year hs-CRP measurement available for three subjects in the high hs-CRP group; one subject was discontinued after Study Visit 2 and two subjects did not complete the 1-year follow-up hs-CRP measurement. The hs-CRP values were not significantly different between baseline and 1 year for the high hs-CRP group ($p = 0.55$), but were nearly significantly higher at 1 year for the low hs-CRP group ($p = 0.051$).

Cytokines

Cytokine analyses were performed on all but two subjects. One subject's synovial fluid sample could not be quantitated and one sample was not sequestered during surgery. All cytokines except IL-2 were detectable in synovial fluid samples and, therefore, IL-2 was omitted from the analysis. The mean value for all cytokines measured, with the exception of CD-40 ligand, were higher in the high hs-CRP group than the low hs-CRP group (Table 2).

Data were determined to be non-normally distributed and, therefore, nonparametric analyses were performed. Spearman correlation coefficients for all subjects combined ranged from –0.31 ($p = 0.0977$) for IL-6 *versus* CD40L, to 0.75 for IL-4 *versus* IL-13 ($p < 0.001$). When data from all subjects were combined, statistically significant correlations occurred for 24 different cytokine comparisons (Table 3). IL-10 and IL-5 were significantly correlated with hs-CRP ($p = 0.0029$ and $p = 0.0137$, respectively) and IL-10 showed the most significant trend toward being a positive predictor for high hs-CRP (i.e. hs-CRP ≥4.0 mg/l; $p = 0.055$) with an AUC of 0.76.

There was a significant difference between the low and high hs-CRP groups for IL-10 (2.81 pg/ml *versus* 6.10 pg/ml, respectively; $p = 0.029$) and a trend toward significance for IL-6 (33.79 pg/ml *versus* 176.28 pg/ml, respectively; $p = 0.079$). Otherwise, there were no significant differences between the low and high hs-CRP groups for any of the cytokines measured (Table 2).

Table 1. Subject demographics and hs-CRP at baseline.

Subject group	Parameter	Baseline values
All subjects combined	*N*	31
	Gender	
	Female	12 (39%)
	Male	19 (61%)
	Age (mean ± SD) (years)	59.3 ± 7.52
	Range (years)	46.5–76.7
	BMI (mean ± SD) (kg/m^2)	27.62 ± 5.54
	Range (kg/m^2)	17.8–40.0
	hs-CRP (mean ± SD) (mg/dl)	4.32 ± 5.63
	Range (mg/dl)	0.3–27.20
Low hs-CRP group	*N*	15
	Gender	
	Female	7 (47%)
	Male	8 (53%)
	Age (Mean ± SD) (years)	58.1 ± 5.84[a]
	Range (years)	49.6–69.3
	BMI (Mean ± SD) (kg/m^2)	24.48 ± 3.93[b]
	Range (kg/m^2)	17.8–32.8
	hs-CRP (Mean ± SD) (mg/dl)	0.55 ± 0.23
	Range (mg/dl)	0.30–1.00
High hs-CRP group	*N*	16
	Gender	
	Female	5 (31%)
	Male	11 (69%)
	Age (mean ± SD) (years)	59.4 ± 8.2[a]
	Range (years)	46.5–76.7
	BMI (mean ± SD) (kg/m^2)	30.48 ± 5.46[b]
	Range (kg/m^2)	23.0–40.0
	hs-CRP (mean ± SD) (mg/dl)	7.86 ± 5.98[c]
	Range (mg/dl)	4.40–27.20

[a]Low *versus* high hs-CRP; age ($p = 0.995$).
[b]Low *versus* high hs-CRP; BMI ($p = 0.001$).
BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; SD, standard deviation.

Bone health

Gross bone appearance (bone health) was evaluated during surgery using a five-point qualitative scale described above. The overall bone health score was based on the surgeon's qualitative assessment, without prior knowledge of hs-CRP level, of bone color, density, and visual presence of cysts and/or necrosis. Of the subjects who had lymphocytes present in their synovium sample, five had a bone score of 1; two had a score of 2; and three had a score of 3. The low hs-CRP group had a significantly higher average bone score than the high hs-CRP group (2.9 *versus* 2.0; $p = 0.014$) indicating better overall bone health.

Figure 1(a) is a representative image, taken during surgery, of bone from a high hs-CRP subject with a bone score of 1 (i.e. poor bone health). In contrast, Figure 1(b) shows a subject with a bone score of 4 who was in the low hs-CRP group.

Histological examination revealed signs of synovitis including lymphocytes in 10 synovium samples and one bone sample, and neutrophils in one bone sample. Nine of the synovium samples that contained lymphocytes were from the high CRP group (one bilateral TKA subject had lymphocytes present in both synovium samples). The subject with lymphocytes present in bone was

Table 2. Mean cytokine values measured in synovial fluid.

	Baseline hs-CRP	CD-40L	IFN-γ	IL-10	IL-12	IL-13	IL-1b	IL-2	IL-2r	IL-4	IL-5	IL-6	IL-8	TNF-α
	mg/l	pg/ml												
All subjects combined														
N[a]	29	29	29	29	29	29	29	29	29	29	29	29	29	29
Mean	4.44	0.32	0.85	4.49	0.40	3.46	6.29	0.00	507.87	0.31	0.40	101.70	1.36	0.49
SD	5.78	1.20	3.54	4.06	1.74	10.50	21.11	0.00	448.48	0.96	1.42	201.51	4.02	0.96
Min	0.30	0.00	0.00	0.70	0.00	0.00	0.00	0.00	42.95	0.00	0.00	0.00	0.00	0.00
Max	27.20	6.17	18.96	19.12	9.31	56.99	111.68	0.00	2189.04	4.27	7.37	854.88	20.98	2.82
Low hs-CRP														
N	14	14	14	14	14	14	14	14	14	14	14	14	14	14
Mean	0.56	0.56	0.17	2.81[c]	0.05	1.68	0.61	0.00	419.51	0.07	0.16	33.79	0.74	0.27
SD	0.24	1.67	0.45	1.53	0.13	2.25	1.11	0.00	363.73	0.13	0.58	41.35	1.69	0.78
High hs-CRP														
N	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Mean	8.22	0.11	1.58	6.10[c]	0.79	5.49	11.91	0.00	562.69	0.56	0.67	176.28	2.08	0.75
SD	6.13	0.40	4.91	5.03	2.40	14.48	28.77	0.00	514.12	1.31	1.90	265.91	5.38	1.10

[a]The number of subjects included in the hs-CRP analysis for cytokines does not include the two subjects for which cytokines were not analyzed; one subject's sample could not be quantitated and one subject's sample was not obtained.
[b]Cytokine results were averaged for all subjects who had more than one sample; this includes subjects for which more than one sample was taken from the same knee and subjects who had one sample taken from each knee (i.e. in the case of bilateral TKAs).
[d]Two-sided *t*-test comparing low and high hs-CRP groups, $p = 0.029$.
IFN, interferon; IL, interleukin; hs-CRP, high-sensitivity C-reactive protein; SD, standard deviation; TKA, total knee arthroplasty; TNF, tumor necrosis factor

also in the high hs-CRP group, as was the subject with neutrophils present.

Radiographic evaluation

Radiograph reviews were performed at 6 weeks, 6 months, and 1 year post-op using the KRSS [Ewald, 1989]. Overall, there were 28 subjects that had 1-year radiographs available for review; 23 subjects with unilateral and 5 subjects with bilateral (10 total), for a total of 33 radiographs. At the 1-year postop visit, there was no lucency in any subject radiographs, and no revisions were required for any subject during the first year of follow up.

Health and functional outcomes: SF-12 Health Survey

SF-12 results were evaluated at baseline (preop), and at 6 months and 1 year postop using categorical scoring for PF, RP, BP, GH, VT, SF, RE, and MH. PCS and MCS values were also computed. Norm-based scoring was used for all SF-12 parameters as well as for PCS and MCS comparisons. The results showed that SF-12 parameters assessed in this study were higher than published norms for subjects with OA in the general population, with the exception of bodily pain, which was lower in the present study population.

There was a statistically significant difference between low and high hs-CRP groups at the baseline evaluations for MCS ($p = 0.0206$), GH ($p = 0.0250$), SF ($p = 0.0174$), and RE ($p = 0.0302$). Otherwise, there were no significant differences between low and high CRP groups at any other visits for any of the SF-12 parameters.

Both the low and high hs-CRP groups showed improvements in PCS following surgery, with the low CRP group showing a greater improvement at 1 year than the high hs-CRP group (Figure 2). MCS worsened postsurgery for the low CRP group, but improved postsurgery for the high CRP group (Figure 3).

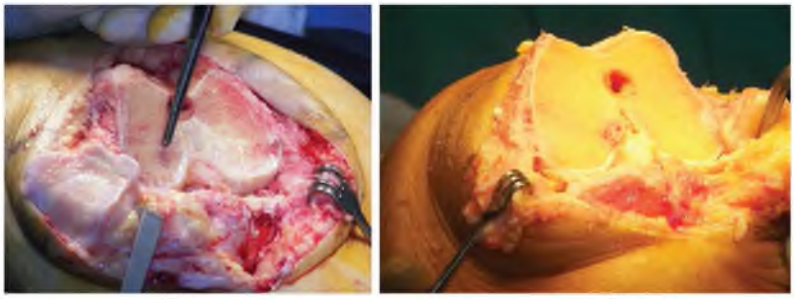
Discussion

Inflammation has been implicated in the pathogenesis of OA, yet the specific correlations between biomarkers of inflammation are still being elucidated.

Table 3. Spearman correlation coefficients and corresponding p-values for synovial fluid cytokines and hs-CRP (all subjects combined).

Variable	hs-CRP	CD 40L	IFN-γ	IL-10	IL-12	IL-13	IL-1b	IL-2r	IL-4	IL-5	IL-6	IL-8	TNF-α
hs-CRP	–												
CD 40L	0.00	–											
(p-value)	0.9952												
IFN-γ	−0.13	−0.14	–										
(p-value)	0.4979	0.4845											
IL-10	0.53	−0.19	−0.02	–									
(p-value)	0.0029	0.3209	0.9359										
IL-12	0.22	−0.15	0.07	0.02	–								
(p-value)	0.2611	0.4254	0.7115	0.9095									
IL-13	0.07	0.02	0.48	0.18	0.56	–							
(p-value)	0.7162	0.938	0.009	0.3623	0.0015								
IL-1b	0.20	−0.09	0.36	0.35	0.38	0.70	–						
(p-value)	0.3006	0.6467	0.0524	0.0614	0.0398	<0.001							
IL-2r	0.19	−0.08	0.11	0.50	−0.14	0.03	0.20	–					
(p-value)	0.3195	0.6919	0.5611	0.0053	0.4738	0.8748	0.2908						
IL-4	0.12	0.02	0.24	0.12	0.52	0.75	0.48	0.06	–				
(p-value)	0.5357	0.9365	0.2143	0.5483	0.0042	<0.001	0.0081	0.7789					
IL-5	0.45	0.16	0.11	0.50	0.10	0.52	0.46	0.34	0.45	–			
(p-value)	0.0137	0.3948	0.5751	0.0056	0.5935	0.0036	0.0131	0.0689	0.0148				
IL-6	0.27	−0.31	0.21	0.49	0.05	0.35	0.30	0.30	0.34	0.40	–		
(p-value)	0.1644	0.0977	0.2813	0.0076	0.7947	0.061	0.1156	0.1108	0.068	0.0319			
IL-8	0.01	−0.26	0.22	0.21	0.11	0.38	0.14	−0.03	0.19	0.21	0.58	–	
(p-value)	0.9419	0.181	0.255	0.2801	0.5785	0.0423	0.4584	0.8639	0.3216	0.2852	0.0009		
TNF-α	0.19	−0.22	0.66	0.17	0.12	0.54	0.36	0.24	0.50	0.48	0.56	0.39	–
(p-value)	0.3233	0.2461	<0.001	0.3761	0.522	0.0027	0.0567	0.2127	0.0056	0.0086	0.0015	0.039	

IFN, interferon; IL, interleukin; hs-CRP, high-sensitivity C-reactive protein; SD, standard deviation; TKA, total knee arthroplasty; TNF, tumor necrosis factor.



(a) (b)

Figure 1. (a) Photograph of representative patient with high hs-CRP. Patient has hypertrophic bone spurs on patella and darkened areas in bone indicative of poor bone quality. (b) Photograph of representative low hs-CRP subject's bone with a bone score of 4. Note the consistency of the color and lack of gross cystic or inflammatory changes.

The primary goal of the present study was to evaluate potential correlations between hs-CRP and postoperative functional outcomes.

In the current study, there was a correlation between patients with elevated serum hs-CRP (≥4.0 mg/dl) and the presence of inflammatory

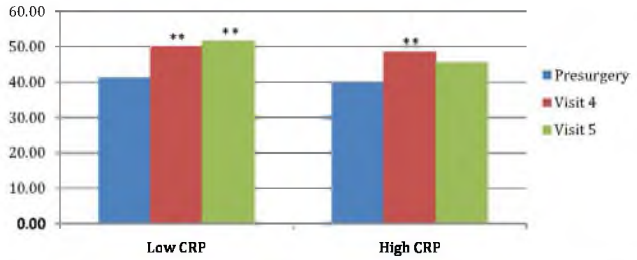


Figure 2. Physical Component Summary (PCS) results by low and high C-reactive protein (CRP) groups (baseline, 6 months postop, and 1 year postop). $^{**}p < 0.05$ compared with baseline (presurgery).

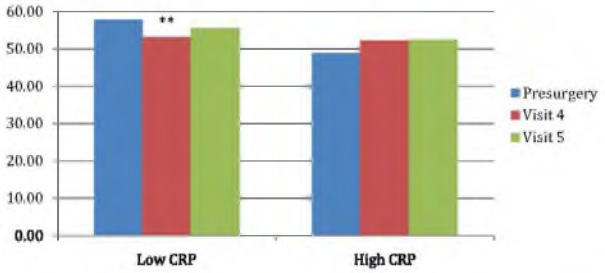


Figure 3. Mental Component Summary (MCS) results by low and high C-reactive protein (CRP) groups (baseline, 6 months postop, and 1 year postop). $^{**}p < 0.05$ compared with baseline (presurgery).

changes in synovium samples taken from the knee joint in patients with OA. Upon histological examination, lymphocytes were present in 10 synovium samples and one bone sample, all but one from the high hs-CRP group. This finding is consistent with other studies suggesting that the presence of inflammatory synovitis in individuals with OA, which includes the infiltration of macrophages and lymphocytes, is indicative of more severe pain and joint dysfunction, and may be more predictive of faster rates of cartilage loss [Sellam and Berenbaum, 2010; Scanzello and Goldring, 2012]. In addition, there was a correlation between bone health (based on gross visual appearance), serum hs-CRP, and synovial fluid cytokines. While these secondary findings lend support for greater localized inflammation in individuals with higher hs-CRP, it is not clear how localized inflammation may have affected functional outcomes postoperatively.

The bone health score used in this study was based on several years of observation by the principal investigator of this study. It became obvious after performing hundreds of TKA surgeries and measuring hs-CRP in subjects undergoing TKA surgery, that there are gross visual differences in bone and tissue quality between subjects with low and high hs-CRP. These observations were further refined based on visual observations including color, presence of cysts or other oxidative changes, and bone density, which is easily discerned via the bone cuts required to install a knee implant. Although the scoring system has not been thoroughly validated, the results of this study provide evidence supporting the potential merit of the scale and the possibility of evaluating bone health through simple observation and clinical experience. Consistent with prior studies, BMI was significantly higher in the high hs-CRP group than the low hs-CRP group. Although this correlation is not an unfamiliar finding [Timpson *et al.* 2010], the results support the growing body of evidence that BMI and obesity are correlated with inflammation, as well as the progression of OA [Conrozier *et al.* 1998, 2000; Sharif *et al.* 2000]. This finding is also an important consideration in the present study, as a higher BMI in

the high hs-CRP group may provide an alternative explanation for the poorer functional outcomes postoperatively in the high hs-CRP group. Support for this explanation are found in a study by Jones and colleagues, where severe obesity was shown to be a significant risk factor for worse pain and functional recovery at 6 months post-TKA [Jones *et al.* 2012], as well as a study by Gandhi and colleagues that showed a correlation between obesity and poorer outcomes post TKA [Gandhi *et al.* 2010]. The authors of the latter study concluded that patient function following joint replacement surgery is negatively affected by metabolic abnormalities which is possibly related to a systemic proinflammatory state. In contrast to these findings, a study by Stevens-Lapsley and colleagues showed no correlation between BMI and functional outcomes at 1, 3, and 6 months post-TKA [Stevens-Lapsley *et al.* 2010]. A potential explanation for the equivocal results is differences in methodology of how functional outcomes were measured, as well as the presence of comorbidities and associated inflammation. These findings highlight the need for additional research to delineate the impact of BMI, metabolic abnormalities, as well as inflammation on relevant functional outcomes, and how postop rehabilitation may be designed to best address these deficits.

Research has also shed light on the association between synovitis and cytokines in the pathogenesis of OA and suggests that cytokines play an important role in the progression of OA [Luyten *et al.* 2006]. To further understand how cytokines may influence the progression and presentation of OA and their potential relationship with hs-CRP, we evaluated 12 cytokines measured in synovial fluid samples in patients with OA undergoing TKA. Results showed a significant difference in IL-10 between the low and high hs-CRP groups, and IL-6 trended toward a significant difference between the two CRP groups. IL-10, in particular, has been shown to have a significantly greater presence in osteoarthritic chondrocytes compared with healthy controls [Iannnone *et al.* 2001] and has been suggested as a potential therapeutic target for OA due to its anti-inflammatory effects and inhibition of IL-1 and TNF-α synthesis [Fernandes *et al.* 2002]. Results from the present study lend further support to the potential role of IL-10 and other cytokines in the pathogenesis of OA.

Radiographic results showed no visible lucency at 1 year in any subject, indicating that the appropriateness of the prostheses used was not significantly affected by the subjects' initial bone health or inflammatory status. Although a higher BMI, and associated hs-CRP, would be expected to be associated with a higher implant failure rate, the highly variable and multifaceted nature of implant failures would dictate a much larger patient population to identify how the parameters investigated in this study may affect the rate of implant failure. Additional research is indeed necessary to delineate how inflammatory processes or expectation of postsurgical functional ability may influence the choice of implant.

Nonetheless, there were differences in the SF-12 health survey results presurgery and postsurgery between the two CRP groups, suggesting that the presence of increased inflammatory processes may affect long-term rehabilitation and physical function. More specifically, quality of life evaluations were performed using the SF-12v2 scoring system, the results of which were consistent with other studies of subjects undergoing TKA. Specifically, Hartley and colleagues showed improvements in the SF-12 physical scores in both primary and revision TKA subjects that were highly statistically significant at 6 months [Hartley *et al.* 2002]. Similarly, in the present study, when all subjects were combined, there was a statistically significant improvement in PCS postsurgery at both 6 and 12 months. In addition, there was greater improvement in physical function for the low hs-CRP group postsurgery, compared with the high hs-CRP group, even though they had similar presurgery PCS scores. The low hs-CRP group achieved a PCS similar to that of the general population postsurgery, whereas the PCS score for the high hs-CRP group remained below the mean values. This is an important finding considering the general, long-term deficits in physical function in TKA patients, and points to the need for modified or improved rehabilitation protocols for patients with elevated CRP.

Overall, these findings may indicate a potentially better long-term prognosis for the low hs-CRP group with regard to physical function, but it is unclear how the mental component of SF-12 factors in. The MCS score declined in the low hs-CRP group at the postsurgical evaluations, but improved, nonsignificantly, in the high hs-CRP group. This may point to improved, presurgical, mental well-being in the low hs-CRP group that was affected negatively by the rehabilitation process postsurgery. At the 1-year visit, the low

hs-CRP group's MCS score increased somewhat compared with the 6-month visit, but was still below the initial level.

The limitations of the study include the small sample size, lack of a healthy control group, lack of validation of the bone scoring system, and follow up of only 1 year postop. Because a healthy control group was not included in this study, it was not possible to determine whether the inflammation observed in this study was a cause or symptom of OA, or a contributing factor to joint degradation. It is suspected that the answer is multifaceted with many inflammatory pathways contributing to and acting in concert to both cause and mitigate inflammatory processes systemically.

It is recognized that the bone score used in this study has not been thoroughly validated and additional research is required to fully understand how gross bone appearance may correlate with overall bone health, and how this information may be used to guide surgical decisions. While the bone scoring method used in this study was validated by two individuals participating in the surgery (the surgeon and physician's assistant, who is also an author on this manuscript), it requires validation by additional, independent surgeons to ensure validity and reliability of the measurement. Future research should evaluate correlations between cytokines in synovial fluid to results in serum. The latter is clearly a more appropriate clinical test that could be distributed to a large number of patients.

This study also discerned a possible link between hs-CRP level and joint pathogenesis and potentially reduced physical function postsurgery. There were clear differences between cytokine levels in the two CRP groups, but the small sample size may have affected the ability to identify additional significant correlations.

Conclusions

The results of this study showed that patients with OA who also had elevated hs-CRP have increased cytokine levels and inflammatory changes indicative of synovitis compared with subjects with OA and lower hs-CRP. The clinical implications of this finding suggest that hs-CRP may be useful, in combination with other indicators of poor outcomes such as BMI and other comorbidities, as a possible predictive variable of severity of OA, rate of progression, and long-term level of postoperative improvement.

While the findings of this study are considered preliminary, markers of inflammation and gross bone health may eventually assist in determining the most appropriate knee replacement implant and rehabilitation protocol for individual patients to ensure optimal recovery and activity post-surgery. The findings point to possible rehabilitation targets postsurgery that extend beyond muscle strength and function, to address overall lifestyle changes to lower hs-CRP and other lifestyle-related indices. Further research is needed to identify long-term implications of inflammation in patients undergoing TKA.

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Conflict of interest statement

Stryker Orthopedics provided funding for activities directly related to this research project, from which Jessica Smith was paid for her activities directly related to this project. Dr Rosenberg also previously received consultancy fees from Stryker Orthopedics for various activities, which are not currently ongoing. There are no other potential conflicts of interest.

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CHAPTER 3

MUSCLE FORCE STEADINESS IN OLDER ADULTS BEFORE AND AFTER TOTAL KNEE ARTHROPLASTY

3.1 Abstract

The ability to control submaximal muscle forces has been shown to be associated with age-related decreases in physical function, such as increased tendency to fall. This study compared quadriceps muscle force steadiness (MFS) in individuals with knee OA before and after total knee arthroplasty (TKA) to an age-matched group of controls. Lower extremity MFS was measured in 13 subjects with knee OA before and at 6 months after TKA (TKA-GROUP) and compared to an age-matched control group (CONTROL-GROUP). MFS was significantly more impaired in the TKA-GROUP at the preoperative, but not postoperative visit, and significantly improved between the pre- and postoperative visits. Further research is warranted to evaluate the relation between this MFS measurement and physical functional performance in those at high risk for falling.

3.2 Introduction

Symptomatic knee osteoarthritis (OA) affects nearly 4.3 million or 12% of adults over the age of 60 in the United States (Dillon, 2006; Hootman et al., 2009). By the year 2030, this number is expected to grow to 25% of adults in the US (Hootman and Helmick 2006), with a corresponding 6-fold increase in the number of total knee arthroplasty (TKA) surgeries from the current annual rate of 500,000 per year (Kurtz et al., 2007; Hootman et al., 2009). TKA has been shown to reduce chronic knee pain associated with OA (Mizner et al., 2005a; Mizner et al., 2005b; Yoshida et al., 2008; Bade et al., 2010), though studies have consistently demonstrated residual mobility deficits linked to reduced quadriceps muscle function (Mizer et al., 2003; Stevens et al., 2003; Mizner et al., 2005a; Mizner et al., 2005b; Mizner et al., 2005c; Meier et al., 2008; Yoshida et al., 2008; Bade et al., 2010). Despite the long-term muscle and mobility deficits, the demand for the pain-reducing TKA procedure continues to increase as does the need to identify modifiable factors that may be linked to suboptimal physical function following surgery (Startzell et al., 2000; Scott, 2005).

Persistent quadriceps weakness in TKA recipients is clinically important as it is coupled to physical function that requires adequate maximal strength and control of submaximal muscle force variability (Enoka et al., 2003; Seynnes O., et al., 2005). Specifically, muscle atrophy, muscle weakness, and neuromuscular activation deficits are all factors that have been implicated in residual postoperative strength impairments (Yan, 1999; Meier et al., 2008). Additionally, declines in proprioception (Skinner et al., 1984), kinesthetic awareness, and other sensory feedback mechanisms, have been linked to slower movement patterns (Darling and Cook, 1987; Cole et al., 1999; Yan, 1999),

decreased power output, and reduced force steadiness (Kinoshita and Francis, 1996; Walker et al., 1997; Christou et al., 2003). The consequences of these adaptations include a reduced ability to exert a steady force output during submaximal contractions, as well as greater variability in movement patterns (Kinoshita and Francis, 1996; Tracy and Enoka, 2002). Indeed, most activities of daily living require submaximal effort, and therefore, the ability to execute these tasks steadily, accurately, and without impairment is important to long-term physical function.

Quadriceps muscle force steadiness (MFS), which represents the ability to maintain constant submaximal muscle forces, has been positively correlated with performance during stair stepping in patients with hip OA (Pua et al., 2010), and with functional performance in elderly women (Seynnes et al., 2005), elderly fallers compared to non-fallers (Tracy and Enoka, 2002), and in individuals with knee OA compared to healthy controls (Hortobagyi et al., 2004). By necessity, TKA surgery disrupts the knee joint capsule and associated mechanoreceptors that contribute to proprioceptive feedback and control of muscle force output. While the removal of intra-articular pathology has a predictable pain reduction effect, the effects on MFS and the ability to perform functional activities highly dependent on sensorimotor feedback remain unclear. The impact of TKA surgery on quadriceps MFS has not, to our knowledge, been described. Muscle force steadiness is a novel measurement in this patient population and may have implications as a rehabilitation target for improving physical function and long-term postoperative outcomes.

Thus, the purpose of this study was to compare MFS of submaximal quadriceps force output in individuals with knee OA before and after TKA, to a group of age-

matched controls with native knees. We hypothesized that preoperatively, the surgical leg would exhibit impaired MFS compared to the control group. Because the effects of TKA surgery on MFS are unknown, we propose the null hypothesis that at 6 months following surgery, MFS would not significantly improve on the surgical leg compared to their preoperative study visit, or the control group.

3.3 Methods

The study was approved by the University of Utah Institutional Review Board (IRB) and all subjects consented to participation prior to enrollment. A total of 16 TKA subjects (TKA-GROUP) were recruited from the University Orthopedic Center (Salt Lake City, UT) and 11 healthy controls (CONTROL-GROUP) with native knees were recruited from local advertisements and the University of Utah Department of Physical Therapy (Salt Lake City, UT) subject database. Subjects included men and women between the ages of 50 and 75 years.

All TKA-GROUP subjects were diagnosed with knee OA, and were scheduled for TKA surgery prior to enrollment. All TKA-GROUP subjects underwent primary TKA by one of two surgeons at a tertiary academic medical center under either a general or spinal anesthetic with a 0.125-0.25% bupivacaine femoral nerve catheter for 48 h and single shot popliteal fossa block. Procedures were performed using a medial parapatellar arthrotomy. Cemented or cementless cruciate retaining femoral components, cemented modular titanium tibial components, and either a cruciate retaining (CR) or anterior stabilized (AS) bearing (Vanguard, BIOMET, Inc., Warsaw, Indiana, USA) were implanted. For the TKA-GROUP, exclusion criteria included rheumatoid arthritis; a body

mass index (BMI) > 40; comorbidities that would have influenced the ability of the subject to perform the study assessments; inability to complete questionnaires secondary to cognitive/language difficulties; history of smoking, or alcohol or drug abuse within the past 1 year; current diagnosis or treatment for cancer, Parkinson's Disease, Multiple Sclerosis, or other neurological conditions; current diagnosis of a chronic inflammatory condition including, but not limited to, lupus or inflammatory bowel disease; and participation in another investigational study involving an exercise protocol <30 days before enrollment in the current study. In the TKA-GROUP subjects, the diagnosis of OA was confirmed preoperatively with radiographs and careful review of past medical conditions. Table 3.1 includes a summary of baseline subject characteristics.

The CONTROL-GROUP, comprised of healthy control subjects with native knees, had little to no knee pain with pain levels < 3 out of 10 on a visual analog scale for walking or stair climbing in either knee. The CONTROL-GROUP also had no history of joint replacement or other joint surgery that would interfere with their normal gait patterns.

Study assessments included quadriceps MFS, as measured by the coefficient of variation (CV) of force during MFS tasks, in an open-chain fashion on a KinCom 500H dynamometer (Isokinetic International, Harrison, TN). Self-report outcome measures of physical activity levels were assessed using the Rapid Assessment of Physical Activity (RAPA) survey at the pre- and postoperative study visits by the TKA-GROUP and by the CONTROL-GROUP at their one study visit.

3.3.1 Lower Extremity Muscle Force Steadiness (MFS)

MFS was quantified by determining the ability to exert a steady submaximal muscle force using a KinCom dynamometer (Isokinetic International, Harrison, TN). The surgical leg for the TKA-GROUP was assessed at two time points: within 2 months prior to surgery and at 6 months postoperatively. For the CONTROL-GROUP, MFS measurements were performed at one time point on the dominant leg only, which was the same as the hand they wrote with. The target force for MFS testing was established first by testing the quadriceps maximal voluntary isometric contraction (MVIC) peak force (N), with the hip flexed to 90 degrees and the knee flexed 45 degrees. Prior to the MVIC test, subjects completed three submaximal practice trials to become familiar with the testing procedure. Each practice trial included a self-reported successive increase in force from between 50% and 75% of their MVIC. Each MVIC test consisted of a 3-second maximal contraction with 1 to 2 min rest between each test. The peak force from the three trials was used to calculate the 50% MVIC target force for MFS testing. Concentric and eccentric MFS was tested across a knee range of motion of 75 to 15 degrees of knee flexion. MFS testing was performed isokinetically at a fixed speed of 15 degrees/second, and data were sampled at 1000 Hz. Thus, a total of 4 seconds of data were collected for each of the concentric and eccentric contractions. The middle 2 seconds (60 to 30 degree ROM) was used for data analysis as a conservative strategy to eliminate transition effects in the first and last 1 second of movement.

For MFS testing, the computer monitor was placed approximately 3 feet in front of the subject and the main lights in the room were dimmed to enhance the visibility of the screen. A bold horizontal target force line representing 50% of MVIC was visible on

the screen. The subject was instructed to exert force against the lever arm attached to their lower leg and match the target force line on the computer monitor as steadily as possible over the entire range of motion. The subject's force was represented by a bold signal that scrolled horizontally from left to right across the screen. Fifty N of force was required to initiate the movement of the lever arm in either concentric or eccentric mode. The same procedure was used for concentric and eccentric MFS testing.

Muscle force steadiness testing included 1) one familiarization trial to become familiar with the testing procedure (not recorded), 2) nine warm-up trials, and 3) up to 15 additional recorded trials that were used for data analysis. The nine warm-up trials were performed to minimize any effects of short-term learning. Criteria for stopping included knee pain greater than or equal to 3 on a 1 to 10 visual analog scale (VAS) scale, with 10 being the highest pain; or if the subject reported fatigue that was significant enough to prevent completion of more trials, even with greater than 5 min of rest. Otherwise, subjects completed all 15 trials.

Following data collection, the concentric and eccentric force-time curves of all the trials were low-pass filtered at 100Hz (Butterworth). The middle 2 seconds (60 deg to 30 deg of knee flexion) was detrended by removing the slope from the data and the standard deviation (*SD*) was calculated. The coefficient of variation of the force was also calculated (CV = *SD* of force/mean of raw force x100). The rationale for the detrending procedure was to remove any relatively slow, drifting deviations away from the mean force. The *SD* of force represents the average absolute fluctuation around the target and the CV is a value normalized to the mean force produced, thus allowing comparison between subjects of different strength levels.

3.3.2 Statistical Analysis

Subject demographics were evaluated using descriptive statistics and compared between groups using a Student's *t*-test, after testing for homogeneity of variance. RAPA scores were also compared between groups using repeated measures analysis of variance (ANOVA) for within-subjects' comparisons across time points, and a univariate ANOVA for comparisons between the TKA-GROUP and CONTROL-GROUP. To eliminate any potential effects from pain and/or fatigue, a two-way repeated measures ANOVA was used to test for study visits × trial interactions. The number of trials for which there were no significant study visit × trial interactions, while maintaining the largest sample size was used for the comparison of MFS between study visits. Comparisons between the pre- and postoperative study visits were performed separately for concentric and eccentric contractions using a repeated measures ANOVA, and between the TKA-GROUP and CONTROL-GROUP using a univariate ANOVA. All statistical tests were performed using a power of 0.80 for accepting the null hypothesis and significance level of 0.05 using SPSS Statistical Software (IBM Corporation).

3.4 Results

Sixteen TKA subjects completed the preoperative study visit and 13 subjects completed the 6-month postoperative study visit. For the 3 subjects that did not complete the postoperative visit, 1 subject moved her surgery to a facility outside the University Orthopedic Center and 1 subject suffered a fall at approximately 4 months following surgery and was, therefore, unable to complete the assessments at the postoperative visit. The third subject underwent TKA on his contralateral knee at 2 months following the

initial surgery. As a result, this subject underwent testing at the postoperative visit, but was excluded from the data analysis presented herein due to potential confounding effects of the second surgery on the function, rehabilitation, and outcomes from the first surgery. Therefore, only the 13 TKA-GROUP subjects that completed both the pre- and postoperative study visits were evaluated for the data analysis.

Table 3.1 includes a summary of baseline subject characteristics. Body mass index (BMI) was significantly lower in the CONTROL-GROUP compared to the TKA-GROUP (23.07 ± 2.16 kg/m^2 vs. 31.29 ± 4.13 kg/m^2; $p < 0.001$) and remained unchanged following surgery for the TKA-GROUP (31.08 ± 4.36 kg/m^2). All subjects in the TKA-GROUP were on at least one drug therapy, with the most prevalent medications prescribed for hypertension, hypercholesterolemia, and Type 2 diabetes. The RAPA survey results showed that preoperatively, the TKA-GROUP was significantly less active than the CONTROL-GROUP (4.23 ± 1.36 vs. 6.27 ± 0.90; $p < 0.001$), with the TKA-GROUP categorized as "under-active, regular" and the CONTROL-GROUP categorized as "active." Postoperatively, the TKA-GROUP did not improve significantly compared to preoperatively (4.23 ± 1.36 vs. 4.69 ± 1.55; $p = 0.36$), and remained significantly less active than the CONTROL-GROUP ($p = 0.007$).

3.4.1 Maximal Voluntary Isometric Contractions

At both the pre- and postoperative study visits, MVIC relative to BMI (MVIC/BMI) was significantly lower in the TKA-GROUP compared to the CONTROL-GROUP. MVIC/BMI for the CONTROL-GROUP was 12.57±3.86 N/BMI compared to the TKA-GROUP at the preoperative study visit (6.64±2.87 N/BMI; $p < 0.001$) and

postoperative study visit (7.84±2.31 N/BMI; $p = 0.001$). Additionally, MVIC/BMI did not significantly improve from the pre- to postoperative study visits in the TKA-GROUP (6.64±2.87 N/BMI vs. 7.84±2.31 N/BMI; $p = 0.18$). Additionally, MVIC/BMI did not significantly improve from the pre- to postoperative study visits in the TKA-GROUP (6.64±2.87 N/BMI vs. 7.84±2.31 N/BMI; $p = 0.18$).

3.4.2 Lower Extremity Muscle Force Steadiness

Preoperatively, 3 of the 13 TKA-GROUP subjects were not able to complete all MFS trials on the surgical leg due to pain and/or fatigue as described above. Postoperatively, all TKA-GROUP subjects were able to complete the MFS trials. For the CONTROL-GROUP, testing was performed on the dominant leg and all subjects completed all MFS trials for both concentric and eccentric contractions.

The first nine MFS trials were used for both concentric and eccentric contractions for comparison between study visits and groups, as these trials showed no study visit × trial interaction while maintaining the largest sample size for comparison. Fig.s 3.1 and 3.2 show the mean MFS by trial number at the pre- and postoperative study visits and for the CONTROL-GROUP for concentric and eccentric contractions, respectively.

Using the mean of nine trials for comparison for both the TKA-GROUP and CONTROL-GROUP, the results showed a significant difference in CV of MFS between the preoperative surgical leg in the TKA-GROUP and the CONTROL-GROUP for concentric (9.88±1.13% vs. 8.29±0.91%; $p = 0.005$), and eccentric contractions (9.23±1.18% vs. 8.03±1.17%; $p = 0.045$), with the leg scheduled for TKA showing less steadiness than the CONTROL-GROUP for both contraction types. Comparisons

between the pre- and postoperative study visits for MFS showed significant improvements on the surgical leg for both concentric contractions (9.88±1.13% vs. 6.82±0.98%; $p = 0.001$) and eccentric contractions (9.23±1.18% vs. 6.62±1.08%; $p = 0.002$) (Fig. 3.3). Postoperatively, the surgical leg showed a significant difference compared to the CONTROL-GROUP for concentric (6.82±0.98% vs. 8.29±0.91%; $p = 0.005$), and eccentric contractions (6.62±1.08 vs. 8.03±1.17%; $p = 0.017$), with the surgical leg showing significantly greater steadiness than the CONTROL-GROUP. Fig. 3.3 shows the comparison of the mean MFS between study visits and groups for both concentric and eccentric contractions.

3.5 Discussion

The purpose of this study was to compare the steadiness of submaximal quadriceps muscle force output in OA patients before and after TKA, with a group of age-matched controls with native knees. As anticipated, MFS in those with knee OA preparing for TKA surgery was greater relative to age- and sex-matched controls, suggesting that MFS during concentric and eccentric contractions is impaired in this population. Contrary to the null hypothesis, however, the MFS deficit was reversed following surgery and the steadiness of submaximal force output improved at the 6-month postoperative visit to a level that exceeded the age-matched group of controls.

Limitations of this study include a relatively small sample size. There were also no controls for subjects' rehabilitation course, duration, or other physical activities between study visits. Despite this, we were able to detect changes in MFS. Additionally, subjects were not BMI-matched and the TKA-GROUP subjects were less active and had

more comorbidities compared to the CONTROL-GROUP. Here, however, we controlled for BMI differences by normalizing strength to BMI similar to previous studies (Lewek et al., 2004; Mizner et al., 2005a; Mizner et al., 2005b; Mizner et al., 2005c) and retained a clinically relevant difference in physical activity levels as exhibited by the RAPA scores.

Since there is evidence that the ability to control submaximal muscle force output is linked to attributes of poor physical function such as falling (Schultz, 1992; Christou et al., 2003; Pua et al., 2010), any changes in MFS may be clinically relevant. In the present study, we hypothesized that the mechanisms that have been suggested to contribute to force fluctuations such as arthrogenic muscle inhibition (AMI) and motor unit discharge variability would have greater impairment in individuals with OA compared to a group of age- and sex-matched healthy controls, and would not significantly improve following TKA due to continued quadriceps muscle impairments.

Acknowledging that joint receptors preferentially respond at the extremes of motion (Pai et al., 1997; Sharma, 1999; Weiler et al., 2000), the postoperative findings were still surprising since the requisite joint capsule disruption with the surgical procedure and continued quadriceps muscles impairments compared to healthy controls did not adversely impact MFS. In fact, it contributed to an improvement in MFS, to levels that exceeded a peer group without knee OA. Additionally, even though normalized maximal knee extensor strength (e.g., MVIC/BMI) in the surgical leg improved from the preoperative to the 6-month postoperative time point, it remained significantly weaker at both the pre-and postoperative study visits compared to the CONTROL-GROUP. These results are consistent with other studies that have reported reduced quadriceps strength in

individuals with symptomatic OA (Hurley et al., 1997; Slemenda et al., 1997; Suter and Herzog, 2000), as well as after TKA surgery compared to healthy, age-matched controls with native knees (Berth et al., 2002; Mizner et al., 2003; Stevens et al., 2003; Hortobagyi et al., 2004; Lewek et al., 2004; Saleh et al., 2005; Yoshida et al., 2008; Bade et al., 2010).

The uncoupling of knee extensor strength and MFS is not surprising, as published data have consistently reported that while increases in strength tend to be accompanied by reductions in force fluctuations, the changes in these two parameters are often not correlated, and are influenced by the specific muscle performing the task as well as the type of muscle contraction (Burnett et al., 2000; Connelly et al., 2000; Graves et al., 2000; Enoka et al., 2003; Hortobagyi et al., 2004). For instance, Hortobagyi et al. found that after 10 weeks of strength training, older adults experienced an increase in quadriceps strength and a reduction in quadriceps force fluctuations during anisometric, but not during isometric contractions. Nonetheless, the same force target was used before and after training (25 N), which represented a different proportion of MVIC, thus reducing the ability to draw definitive conclusions about the relationship between the two measurements (Hortobagyi et al., 2001). In a study by the same author, similar steadiness (CV of force) was observed at 50-N and 100-N force targets in individuals with knee OA, even though the target force represented a variable percentage of their MVIC (Hortobagyi et al., 2001). Moreover, Tracy et al. showed improvements in anisometric force steadiness of the quadriceps muscle following 16 weeks of strength and/or steadiness training with heavy loads in older adults, but again, the changes in muscle strength and force fluctuations experienced by subjects were unrelated (Tracy et al., 2004).

The findings of the present study combined with previously published reports highlight the multifactorial contributors to muscle force fluctuations (Galganski et al., 1993; Burnett et al., 2000; Tracy and Enoka, 2002; Enoka et al., 2003). The complexity of these interactions is emphasized by the discrepancies in published data and the wide-ranging methodologies and patient populations investigated. In the present study, only one level of force was utilized to assess MFS (50% of maximum), which precluded the ability to compare submaximal force steadiness at different relative percentages of MVIC. Nonetheless, the target force chosen for this study was toward the upper range of previous reports (Graves et al., 2000; Laidlaw et al., 2000; Hortobagyi et al., 2001; Hortobagyi et al., 2004; Pua et al., 2010) and therefore would be expected to be less sensitive to the effects of motor unit discharge variability on the magnitude of force fluctuations. This would suggest a possible greater dependence of the results on the effects of TKA, as opposed to factors that may be attributed to age and/or sex.

Furthermore, several studies have identified differences in steadiness between concentric and eccentric contractions, with shortening contractions tending to show greater steadiness, especially in older adults (Burnett et al., 2000; Graves et al., 2000; Hortobagyi et al., 2004). From a physiological perspective, Burnett et al. proposed that reduced steadiness during lengthening anisometric contractions is likely due to the characteristics of the most recently recruited motor units, as well as relative activation of the agonist and antagonist muscles. More recently, however, Duchateau and Baudry (Duchateau and Baudry, 2013) present alternative mechanisms to explain the neural control of eccentric contractions. In particular, even though a similar strategy is employed to activate motor neurons for different contraction types, eccentric contractions are

associated with reduced voluntary muscle activation and motor unit discharge rate compared to concentric contractions. In addition, there is evidence to suggest that there are eccentric-specific neural control mechanisms that are employed during submaximal eccentric contractions (Fang et al., 2001). In the present study, subjects displayed similar improvements in eccentric and concentric contractions from the pre- to postoperative study visits in the surgical leg, as well as improved concentric and eccentric steadiness at the postoperative visit to the CONTROL-GROUP. One potential explanation for these findings is the contraction velocity used during the anisometric contractions of this investigation. Specifically, the rate of contraction has been implicated in the ability to control submaximal forces with the magnitude of force fluctuations greater at higher speeds (Christou et al., 2003). In the present study, a rate of contraction of 15 deg/sec was used for both concentric and eccentric contractions, which is considered relatively slow compared to speeds typically employed to perform normal functional tasks. Thus, the relatively slow rate of contraction may have attenuated some of the force fluctuations that would have been expected during eccentric contractions had the rate of contraction been higher. Another explanation, based on the discussion set forth by Duchateau (Duchateau and Baudry, 2013), suggests a positive effect of TKA surgery on voluntary muscle activation during eccentric contractions and muscle-mediated proprioception that exceeds the contribution from articular mechanoreceptors.

Finally, the possibility that the postoperative MFS results were an anomaly was considered, especially considering the significant postoperative improvement relative to the CONTROL-GROUP. However, the consistency of the preoperative results with those presented by Hortobagyi et al. suggests otherwise (Hortobagyi et al., 2004). In particular,

Hortobagyi showed similar differences in force steadiness between individuals with knee OA and healthy controls, with OA patients showing a weakened ability to produce force, as well as less steady concentric and eccentric force production compared to healthy controls (Burnett et al., 2000; Hortobagyi et al., 2004). In patients with knee OA, the ubiquitous finding of quadriceps weakness compared to healthy controls without OA and associated diminished voluntary muscle activation and proprioceptive acuity has been attributed to reduced quadriceps motorneuron excitability (Hurley et al., 1997), a characteristic that may provide some explanation for the preoperative results of this study. More specifically, evidence suggests that damage to articular mechanoreceptors due to OA is associated with abnormal afferent information, which subsequently reduces the excitability of α-motorneurons and hence voluntary muscle activation. Because afferent fibers also project onto γ-motorneurons, which affect muscle spindle sensitivity, there is a potential corresponding effect on proprioceptive acuity regulated by muscle spindles (Hurley et al., 1997). While specific measures of proprioception and muscle activation were not evaluated in the present study, the hypotheses offered by Hurley et al. (Hurley et al., 1997) and later described by Rice et al. (Rice and McNair, 2010) is believed to be consistent with the preoperative findings in the present study. The surgical intervention, TKA, explicitly results in the removal of damaged tissue, but also improves range of motion and reduces pain, all of which have been reported to positively affect proprioceptive feedback in individuals with OA (Barrack, 1983; Bade et al., 2010). Although these consequences of TKA do not entirely explain the significant improvements in MFS following surgery, they may provide some justification for the

overall improvement in muscle control in the absence of significant strength improvements.

3.6 Conclusions

Total knee arthroplasty, as a surgical intervention for individuals with OA, appears to provide benefits for improving the ability to control submaximal muscle forces, independent of quadriceps strength improvements. A better understanding of how these changes in motor control correlate with other functional performance parameters could direct the development of future intervention strategies and improve long-term TKA outcomes.

3.7 Contributions

All patients recruited for this study were from the practices of Christopher Peters, MD and Christopher Pelt, MD of the University Orthopedic Center (Salt Lake City, Utah).

Table 3.1. Baseline subject demographics; preoperative TKA-GROUP vs. CONTROL-GROUP

Variable	TKA-GROUP (*n*=13)	CONTROL-GROUP (*n*=11)	*p*-value [a]
Age (yrs)	62.71 (6.84)	62.19 (8.61)	0.99
Height (m)	1.67 (0.09)	1.64 (0.10)	0.52
Weight (kg)	86.40 (11.73)	62.15 (10.48)	<0.001
BMI (kg/m^2)	30.96 (4.14)	23.07 (2.16)	<0.001
Gender (% Males)	15%	18%	-
RAPA[b]	4.23 (1.36)	6.27 (0.90)	<0.001

*Data presented as mean (± *SD*)

[a] *p*-value represents the comparison of preoperative TKA-GROUP vs. CONTROL-GROUP.

[b] RAPA scale is 0-7, with 7 being the highest level of activity.

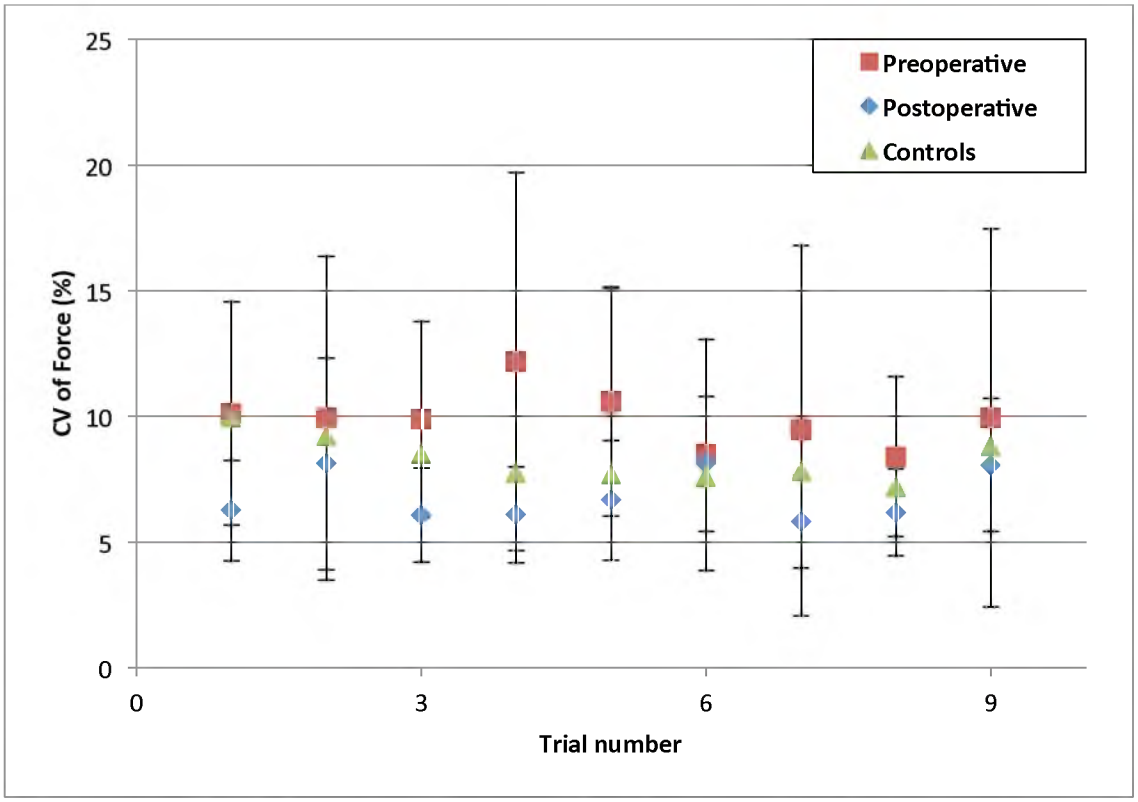

Fig. 3.1. CV of MFS for concentric contractions by trial number for the TKA-GROUP at the pre- and postoperative study visits and CONTROL-GROUP.

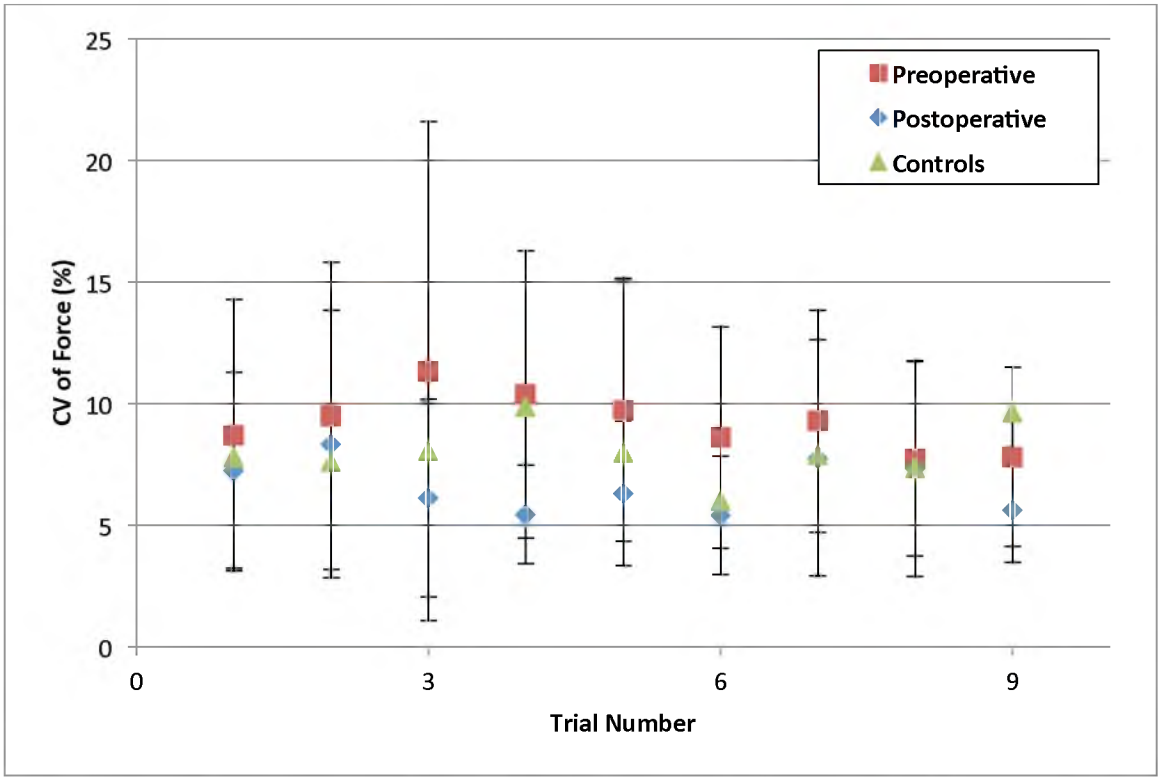

Fig. 3.2. CV of MFS for eccentric contractions by trial number for the TKA-GROUP at the pre- and postoperative study visits and CONTROL-GROUP.

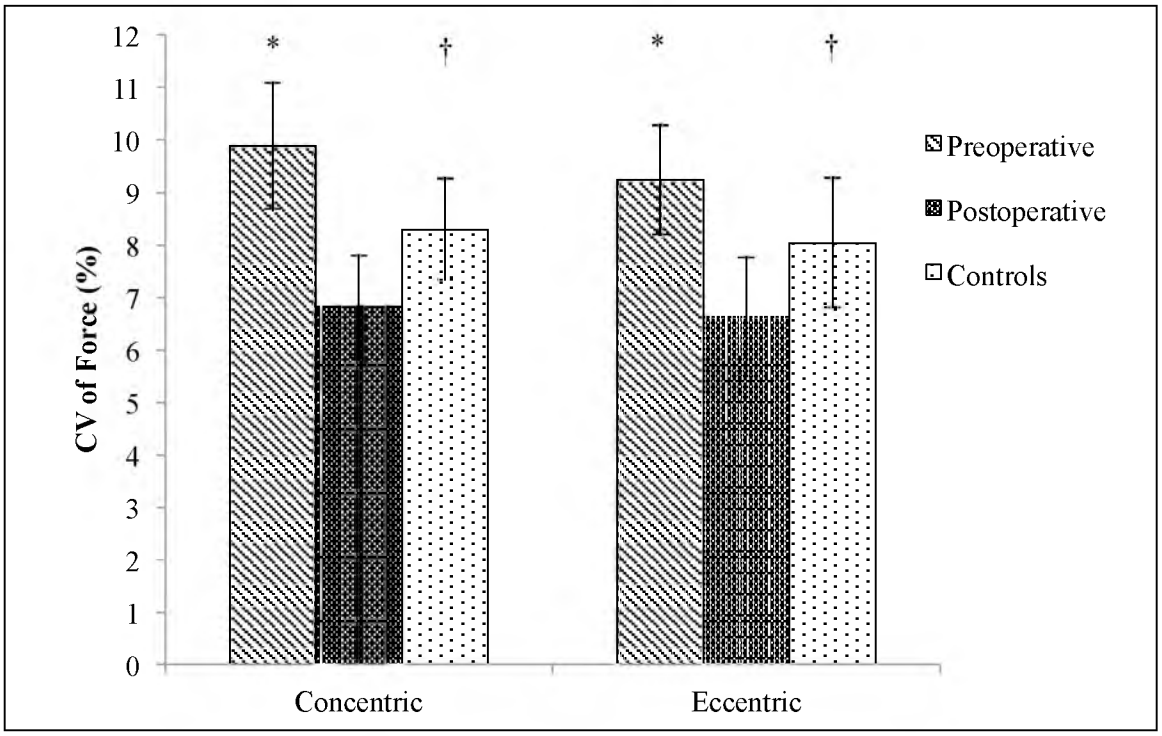

Fig. 3.3. Comparison of CV of MFS results by group and study visit for concentric and eccentric contractions. Data represent the mean of 9 trials at each time point. *$p < 0.01$; Concentric & eccentric preoperative vs. postoperative TKA-GROUP. †$p < 0.05$; Concentric & eccentric pre- and postoperative TKA-GROUP vs. CONTROL-GROUP. n=10 for TKA-GROUP, n=11 for CONTROL-GROUP for all comparisons.

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CHAPTER 4

VARIABILITY DURING GAIT AND STAIR STEPPING BEFORE AND AFTER TOTAL KNEE ARTHROPLASTY

4.1 Abstract

Measures of gait variability have been correlated with risk of falling, but have not been investigated during other functional tasks such as stair stepping or in individuals who have undergone total knee arthroplasty (TKA). The purpose of this study was to compare stance time variability (STV) during level walking and stair stepping in older adults with osteoarthritis (OA) before and after TKA, and to a group of healthy controls without OA. We also investigated potential correlations in STV between gait and stair stepping in the TKA-GROUP. Gait function was evaluated using the GAITRite system (CIR Systems, Sparta, NJ) and stair stepping was evaluated on an instrumented, three-stair, AMTI Force Platform Stairway using two AMTI OR-6 series force platforms (AMTI; Watertown, MA, USA). Results showed a significant reduction in STV during gait between pre- and postoperative visits. Postoperatively, STV during stair descent was significantly greater in the TKA-GROUP compared to the CONTROL-GROUP, but there were no significant correlations in STV between gait and stair stepping. Variability during stair stepping, like STV during level walking, may provide an important

rehabilitation target for individuals following TKA and may represent another parameter that may predict future falls and declines in functional mobility.

4.2 Introduction

The symptoms associated with knee osteoarthritis (OA) include pain, swelling, and loss of motion, often resulting in restricted activity and loss of independence during activities of daily living (Crepaldi and Punzi., 2003; Punzi and Oliviero, 2005). As a result, increasing numbers of individuals with end-stage OA are opting to undergo surgical, total knee arthroplasty (TKA) procedure (Yan, 1999). TKA can effectively reduce pain and restore many, though not all, functional abilities, with improvements in muscle strength and physical function, particularly in the quadriceps muscles and during stair stepping, respectively, typically maintaining deficits compared to a cohort of age-matched, healthy controls without OA (Scott, 2005; Cauley et al., 2007; Hamer and Molloy, 2009;).

Gait, in particular, is a complex, coordinated task that requires contribution from and interaction between both central and peripheral neuromuscular control mechanisms. While there is a growing body of evidence to suggest that gait parameters can be used to predict long-term risk of falling and mobility deficits in different populations (Maki, 1997; Lewek et al., 2006; Brach et al., 2008; Brach et al., 2010; Yakhdani et al., 2010; Callisaya et al., 2011; Kiss, 2011; Montero-Odasso et al., 2011; Kiss et al., 2012), there is a relative lack of data on how these parameters are affected by TKA and whether they can be used to predict long-term outcomes related to physical function.

Individuals with knee OA exhibit quadriceps weakness, inhibition, and associated dysfunction, as well as impaired neural control and proprioception (Barrack et al., 1983; Swanik et al., 2000; Brandt, 2004), which have been suggested to contribute to altered spatio-temporal, kinematic, and kinetic gait patterns compared to healthy controls (Suter and Herzog, 2000; Lewek et al., 2006; Hausdorff, 2007; Brach et al., 2010; Yakhdani et al., 2010; Kiss, 2011). Specifically, knee OA is associated with a distinctive gait pattern which includes slower gait speed and cadence, reduced stride length, and altered kinematics and kinetics during the loading phase of the gait cycle (Suter and Herzog, 2000; Lewek et al., 2006; Brach et al., 2008). More recently, researchers have identified stance time variability (STV) as a particularly important measure as it has been shown to be highly correlated with fall risk and central nervous system (CNS) impairment in older adults, even after consideration for gait speed (Kinoshita and Francis, 1996; Maki, 1997; Hausdorff, 2007; Brach et al., 2008). Other measures of gait variability have also been correlated with severity of OA (Kiss, 2011), as well as risk of future falls and gait instability before and after TKA (Yakhdani et al., 2010; Hatfield et al., 2011).

Since falls occurring on stairs are common, and falls during stair descent outnumber falls during stair ascent (Startzell et al., 2000; Scott, 2005), a characterization of variability during stair stepping is warranted. Variability during stair stepping, similar to variability during level walking, may provide an important rehabilitation target for individuals following TKA, as well as provide another parameter that may predict future falls and declines in functional mobility. While prior studies have shown that TKA influences gait parameters (Fuchs et al., 2002; Smith et al., 2006; Bejek et al., 2011; Catani et al., 2012), to our knowledge, variability in gait parameters has not been

correlated with deficits during other functional tasks associated with falling, such as stair stepping, before and after TKA.

Thus, the purpose of this study was to: 1) investigate gait variability, as assessed by STV, during level walking and stair ascent and descent in older adults with OA before and at 6 months after TKA, and compare to an age- and sex-matched group of healthy controls with native knees, and 2) evaluate the relationship of STV between level walking and stair ascent and descent before and after TKA.

We hypothesized that 1) preoperatively, the surgical leg would exhibit significantly greater STV during both level walking and stair ascent and descent than at 6 months postoperatively; 2) preoperatively, the surgical leg would exhibit greater STV during level walking and stair ascent and descent than a group of healthy controls with native knees; 3) postoperatively, the surgical leg would exhibit similar STV during level walking and stair stepping as a group of healthy controls; and 4) there would be a significant correlation in the TKA-GROUP between STV during level walking and STV during stair ascent and stair descent at both the pre- and postoperative study visits.

4.3 Methods

The study was approved by the University of Utah Institutional Review Board (IRB) and all subjects consented to participation prior to enrollment. A total of 16 TKA subjects (TKA-GROUP) were recruited from the University Orthopedic Center (Salt Lake City, UT) and 11 healthy controls (CONTROL-GROUP) with native knees were recruited from local advertisements and the University of Utah Department of Physical Therapy (Salt Lake City, UT) subject database. Subjects included men and women

between the ages of 50 and 75 years. The CONTROL-GROUP, making up the healthy control subjects with native knees, had knee pain levels < 3 on a visual analog scale for walking or stair climbing in either knee and no history of joint replacement or other joint surgery that would interfere with their normal gait patterns. See Table 4.1 for subject characteristics including both the preoperative and postoperative study visits for the TKA-GROUP.

All TKA-GROUP subjects were diagnosed with knee OA, and were scheduled for TKA surgery. All TKA-GROUP subjects underwent a primary, unilateral TKA by one of two surgeons at a tertiary academic medical center under either a general or spinal anesthetic with a 0.125-0.25% bupivacaine femoral nerve catheter for 48 h and single shot popliteal fossa block. All procedures were performed using a medial parapatellar arthrotomy. Cemented or cementless cruciate retaining (CR) femoral components, cemented modular titanium tibial components, and either a CR or anterior stabilized (AS) bearing (Vanguard, BIOMET, Inc., Warsaw, Indiana, USA) were implanted. For the TKA-GROUP, exclusion criteria included rheumatoid arthritis; a body mass index (BMI) > 40; comorbidities that would have influenced the ability of the subject to perform the study assessments; inability to complete questionnaires secondary to cognitive/language difficulties; history of smoking, or alcohol or drug abuse within the past 1 year; current diagnosis or treatment for cancer, Parkinson disease, multiple sclerosis, or other neurological conditions; or current diagnosis of a chronic inflammatory condition including, but not limited to, lupus or inflammatory bowel disease; and participation in another investigational study involving an exercise protocol <30 days before enrollment

in the current study. In the TKA-GROUP subjects, the diagnosis of OA was confirmed preoperatively with radiographs and careful review of past medical conditions.

TKA subjects were also characterized using the Lower Extremity Functional Scale (LEFS) and the SF-36 Health Outcomes survey at both the pre- and postoperative study visits. The TKA-GROUP completed the surveys at both time points, and the CONTROL-GROUP completed the SF-36 at their one study visit. LEFS was not completed by the CONTROL-GROUP because it is used to measure dysfunction related to lower extremity conditions, which they did not have.

Each subject's quadriceps maximal voluntary isometric contraction (MVIC) peak force (N) was evaluated pre- and postoperatively on a KinCom 500H dynamometer (Isokinetic International, Harrison, TN, USA) with the hip flexed to 90 degrees and the knee flexed to 45 degrees. Prior to the MVIC test, subjects completed three submaximal practice trials to become familiar with the testing procedure. A total of three consecutive MVIC tests were then recorded that consisted of a 3-second maximal contraction with 1 to 2 min rest between each test. The highest of the three recorded MVIC values was used for data analysis.

4.3.1 Variability during Level Walking

Gait assessments were measured during level walking using the GAITRite system (CIR Systems, Inc, Sparta, NJ, USA), which captures both temporal and spatial parameters. The GAITRITE mat consists of a 16 foot long instrumented walkway that contains pressure sensors along the mat. All subjects performed 5 or 6 test walks per visit and for each test, the mean and coefficient of variation (CV) of STV, stride length, step

time, gait velocity, step velocity, and cadence were evaluated. Stride length, step time, gait velocity, step velocity, and cadence were measured to characterize subjects' overall gait patterns. The mean value from all tests for each gait parameter was used for statistical analysis. The same protocol was used for both groups as well as study visits for the TKA-GROUP.

4.3.2 Variability during Stair Stepping

Assessments of stair stepping performance were performed in the Motion Capture Core (MoCap) Facility at the University of Utah, Department of Physical Therapy. The facility includes a 10 camera Vicon motion analysis system (200 Hz), two AMTI OR-6 series force platforms (1000 Hz; Watertown, MA, USA), and a Force Platform Stairway (AMTI; Watertown, MA, USA), which consisted of three instrumented steps rigidly connected to the AMTI force platforms to capture kinematics and kinetics during stair ascent and descent.

For testing on the stairs, participants wore a form-fitting top and bottom, and shoes that were constrained on their feet (i.e., sandals were not allowed). A custom MATLAB program (The MathWorks, Nattick, MA, USA) was used to correlate kinetics and temporal data to confirm the onset and offset of stance time. Participants were asked to perform the stair climbing tasks, which included a total of eight trials. For the stair stepping test, subjects were asked to walk, step over step, either up or down the stairs, at a self-selected pace (i.e., 2 trials up and 2 trials down, starting on the right leg; 2 trials up and 2 trials down, starting on the left leg).

Participants were supervised closely during all trials with an adequate amount of rest to prevent fatigue and/or missteps during testing. A handrail was available on the side of the stairs for the subject to use if necessary. Subjects were allowed to use the handrail for balance, but if they used it for support, the trial was disqualified and an additional trial was performed if the subject was able. Trial disqualification also occurred for stair ascent or descent trials that were not performed "step over step" for all three steps.

The CV of STV was calculated for stair ascent and stair descent for the surgical leg in the TKA-GROUP and in both legs for the CONTROL-GROUP (CV = standard deviation/mean × 100). For the purpose of calculating STV, each trial began upon first contact with the step and ended with last contact of the same foot (i.e., toe off). This stance period used on the stairs corresponds to the same stance period calculated for STV during level walking.

For the TKA-GROUP, the CV of STV was calculated for the surgical leg and at both time points (preoperatively and at 6 months postoperatively). For the CONTROL-GROUP, measures of the CV of STV were combined for both legs and compared to the TKA-GROUP. As a safety measure, knee pain was assessed at random time points during the stair stepping testing procedure by asking the subject to rank their perceived amount of pain on a visual analog scale (0-10, with 10 being the worst, or most excruciating pain imaginable). If the subject had pain greater than or equal to 3 on a 10 point VAS, or verbalized that they were in too much pain or too fatigued to continue, a rest period of up to 5 min was provided, after which if the subject's status did not change, the testing procedure was stopped.

4.3.3 Statistical Analysis

Subject demographics were evaluated using descriptive statistics and compared between groups using a Student's *t*-test, after testing for homogeneity of variance. Pre- and postoperative parameters, including CV of STV during level walking and stair stepping, and means of step length, stride length, stride velocity, gait velocity, and cadence during gait were compared between the CONTROL-GROUP and the TKA-GROUP using a one-way analysis of variance (ANOVA).

Comparisons between pre- and postoperative time points were performed using repeated measures ANOVA. Correlations were evaluated between CV of STV during level walking and stair ascent and descent at both the pre- and postoperative study visits using Spearman's correlations, with Bonferroni corrections employed for multiple comparisons. Self-report outcome measures were also used to characterize the subjects between study groups and within the TKA-GROUP at different time points. Comparisons between self-report outcome measures were performed using a one-way ANOVA for mean differences between groups (TKA-GROUP vs. CONTROL-GROUP) and repeated measures ANOVA for comparisons between time points (preoperative vs. postoperative study visits). A significance level of 0.05 was used for all comparisons, and power of 0.80 to accept the null hypothesis.

4.4 Results

4.4.1 Subject Demographics

Of the 16 TKA subjects enrolled, all completed the preoperative study visit and 13 subjects completed the 6-month postoperative study visit. For the 3 subjects that did

not complete the postoperative visit, 1 subject moved her surgery to a facility outside the University Orthopedic Center, rendering the subject ineligible for the study, and 1 subject suffered a fall at approximately 4 months following surgery and was, therefore, unable to complete the assessments at the postoperative visit. The third subject underwent TKA on his contralateral knee at 2 months following the initial surgery. As a result, this subject underwent testing at the postoperative visit, but was excluded from the data analysis presented herein due to potential confounding effects of the second surgery on the function, rehabilitation, and outcomes from the first surgery. Therefore, only the 13 TKA-GROUP subjects that completed both the pre- and postoperative study visits were included in the data analysis. All 13 subjects were able to perform the gait analysis; however, only 9 subjects were able to complete a "step-over-step" strategy on the stairs at the preoperative study visit. Therefore, for the purposes of stair stepping analysis, a total of 9 subjects in the TKA-GROUP were used for data analysis.

Table 4.1 includes a summary of baseline subject demographics for both the TKA-GROUP and CONTROL-GROUP. BMI was significantly lower in the CONTROL-GROUP compared to the TKA-GROUP (23.07±2.16 kg/m^2 vs. 30.96±4.14 kg/m^2; $p <$ 0.001), and remained essentially the same at the postoperative study visit for the TKA-GROUP (31.08±4.36 kg/m^2). Weight also remained the same between the pre- and postoperative study visits (86.40±11.73 vs. 86.57±10.26 kg; $p = 0.95$). All subjects in the TKA-GROUP were on at least one drug therapy, with the most prevalent medications prescribed for hypertension, hypercholesterolemia, and Type 2 diabetes.

4.4.2 Maximal Voluntary Isometric Contractions

At both the pre- and postoperative study visits, MVIC relative to BMI (MVIC/BMI) was significantly lower in the TKA-GROUP compared to the CONTROL-GROUP. MVIC/BMI for the CONTROL-GROUP was 12.57±3.86 N/BMI compared to the preoperative study visit (6.64±2.87 N/BMI; $p < 0.001$) and postoperative study visit (7.84±2.31 N/BMI; $p = 0.001$). Additionally, MVIC/BMI did not significantly improve from the pre- to postoperative study visits in the TKA-GROUP (6.64±2.87 N/BMI vs. 7.84±2.31 N/BMI; $p = 0.18$).

4.4.3 Self-Report Outcome Measures

For self-report outcome measures, LEFS improved significantly from the pre- to postoperative study visits (40.08±16.58 vs. 57.69±11.99; $p < 0.001$) with a higher score indicating greater function. The results of the SF-36 health outcomes survey were evaluated using the physical component summary (PCS) and mental component summary (MCS) scores. The PCS is an average of responses for physical functioning, role physical, bodily pain, and general health in the SF-36 survey, whereas MCS is an average of responses for vitality, social functioning, role emotional, and mental health. The PCS score increased significantly between pre- and postoperative study visits (36.06±8.67 vs. 48.49±6.03; $p < 0.001$), but remained significantly lower than the CONTROL-GROUP at the preoperative time point (36.06±8.67 vs. 58.22±2.96; $p < 0.001$) and postoperative time point (48.49±6.03 vs. 58.22±2.96; $p < 0.001$). Also, the percentage of subjects below the general population norm for PCS decreased from 85% to 23% from the pre- to postoperative study visits, indicating substantial improvement relative to the general

population for this measure. The MCS of the SF-36 survey also improved in the TKA-GROUP, but not significantly, from the pre- to postoperative study visits, with the percentage below the general population norm decreasing from 31% to 8%, indicating comparable scores relative to the general population. There were no significant differences between the TKA-GROUP and CONTROL-GROUP for MCS at either the pre- or postoperative study visits. Fig. 4.1 includes a summary of self-report outcome measures.

4.4.4 General Gait Parameters

The mean ± SD of gait velocity, cadence, stride velocity, stride length, and step length for the TKA-GROUP and CONTROL-GROUP are included in Table 4.2. Overall, gait velocity, cadence, and stride velocity significantly increased from the pre- to postoperative time points, but remained significantly lower than the CONTROL-GROUP at both study visits. The TKA-GROUP also exhibited significantly longer stride length from the pre- to postoperative study visit, and was comparable to the CONTROL-GROUP at the postoperative study visit (Table 4.2). Step length was not significantly different between study visits or compared to the CONTROL-GROUP at either visit.

4.4.5 Variability during Level Walking and Stair Stepping

In the TKA-GROUP, the CV of stance time during level walking declined significantly after surgery (3.07% vs. 2.16%; $p = 0.004$) and was significantly lower at the postoperative study visit compared to the CONTROL-GROUP (2.16% vs. 4.80%; $p = 0.024$). In addition, the CV of STV during stair descent was significantly higher at the

postoperative study visit compared to the CONTROL-GROUP (14.42% vs. 7.39%; p = 0.007), but was not significantly different between the pre- and postoperative visits (p = 0.535), or between the preoperative study visit and CONTROL-GROUP (p = 0.090). For stair ascent, the CV of STV increased, but not significantly, between study visits (p = 0.661) and was not significantly different compared to the CONTROL-GROUP at either visit. Fig. 4.2 shows the mean values of the CV of stance time for level walking and stair stepping for the TKA-GROUP and CONTROL-GROUP.

Correlations between the CV of stance time during level walking, stair ascent, and stair descent were also evaluated to identify relationships between the two measures. The data were not normally distributed and therefore, Spearman's correlation coefficients were used. The only significant correlation was between the pre- and postoperative study visits for STV during level walking (ρ = 0.56; p = 0.046). Otherwise, there were no significant correlations between the CV of STV between level walking and stair ascent and descent or between time points. Table 4.3 includes correlation coefficients and significance levels for STV during level walking and stair stepping.

4.5 Discussion

The purpose of this study was to compare the CV of stance time during level walking and stair ascent and descent in older adults with OA before and at 6 months following TKA, and to compare to a group of age- and sex-matched healthy controls with native knees. We also evaluated the relationship between the CV of stance time during level walking and stair stepping in subjects with OA before and at 6 months following TKA.

The results of this study showed that after TKA surgery, STV during level walking declined, to a level less than the CONTROL-GROUP, although a similar effect during stair stepping did not occur. However, a significant difference in STV during stair descent was noted between those who received a TKA and the CONTROL-GROUP, with the TKA-GROUP exhibiting significantly greater variability at the postoperative study visit.

The significant decline in variability during level walking in the surgical leg from the pre- to postoperative time points was anticipated, as a similar finding was reported by Yakhdani et al. (Yakhdani et al., 2010) who showed that variability during treadmill walking in TKA recipients was reduced compared to controls preoperatively, and was even lower postoperatively. Nonetheless, the absence of any meaningful change in variability during stair ascent and stair descent between the pre- and postoperative study visits in the present study was contrary to our hypothesis that TKA surgery would result in improved control during stair ascent and descent. We did find, however, that other measures of gait characteristics including gait velocity, cadence, stride velocity, stride length, and step length were consistent with prior studies of individuals with OA (Hurley et al., 1997; Suter and Herzog, 2000; Yakhdani et al., 2010).

In a previous report by Yakhdani (Yakhdani et al., 2010) TKA recipients had reduced gait variability, as evaluated by the knee angular velocity during the first 10% of stance, which was less than controls, and coincided with a reduced risk of falling (Yakhdani et al., 2010). In the present study, the findings of reduced gait variability following TKA during level walking are consistent with those observed by Yakhdani, and while the current study did not specifically investigate risk of falling, we believe that

the consistency of these findings of less variability postoperatively suggest that reducing variability may be a strategy to reduce potential fall risk in subjects of the present study. Our results showed an average postoperative decline in CV of stance time during level walking of 26.4% with 11 of the 13 subjects exhibiting a decline at the postoperative visit. Regardless, the explanation for the significant decline in variability to a level below healthy controls remains unclear. Based on the idea that a certain level of flexibility and adaption between coordinated joint movements is required to perform a given task, it may be that TKA surgery and the associated knee implant results in kinematic constraints on this motion, thus resulting in less flexibility in movement patterns.

The absence of a reduction in STV during stair ascent and descent, and corresponding lack of a relationship in STV between level walking and stair stepping at both the pre- and postoperative study visits was unexpected. Considering the demanding nature of stair stepping on the quadriceps muscles, the muscle and mobility deficits that are typically present following TKA surgery are likely contributors to the postoperative STV findings during stair stepping. While subjects with OA have been shown to use compensatory joint coordination strategies during gait (Suter and Herzog, 2000), it was expected that these strategies would diminish following TKA, and that the variability would become more similar to subjects with native knees. Notwithstanding, this was not realized in the present study, suggesting that mechanisms contributing to quadriceps deficits may have been a greater contribution to the absence of improvement in variability during stair stepping tasks following TKA.

Furthermore, mechanisms used by subjects to reduce variability during level walking have been suggested to include slowing down, paying more attention, and/or

stiffening the joint through co-contraction (Lewek et al., 2006; Leitner et al., 2007; Allali et al., 2008; Yakhdani et al., 2010), Given that subjects in the present study had a significant increase in gait speed and cadence postoperatively, this is an unlikely source of the change in variability. Level of attention and co-contraction were not measured in the present study, and therefore, cannot necessarily be ruled out as potential contributors. Further research is certainly warranted to investigate how these strategies may influence STV during various functional tasks.

Finally, the relative change in the self-report outcome measures observed in this study between pre- and postoperative study visits was consistent with prior studies (Graves et al., 2000; Hartley et al., 2002), as well as with the STV and MVIC findings observed in the present work. There was an overall improvement in LEFS and SF-36 PCS from the pre- to postoperative time points, but PCS remained significantly lower compared to the healthy controls. MCS, on the other hand, was comparable to the CONTROL-GROUP at both study visits.

Limitations of this study include a relatively small sample size and lack of specific inclusion criteria for individuals with a known history of falling. Subjects were also not controlled for their rehabilitation course, duration, or other physical activities between study visits. Additionally, despite the inclusion criteria of BMI < 40, subjects were not BMI-matched, and the TKA-GROUP was less active and had more comorbidities compared to the CONTROL-GROUP, which may have resulted in some bias in the results.

In summary, TKA subjects had a significant reduction in STV during level walking between the pre- and postoperative study visits, although we found no significant

correlation in STV between level walking and stair stepping. STV during stair descent was significantly greater at the postoperative study visit compared to controls. The potential significance of these findings are evident in that we believe that variability during stair stepping, similar to STV during level walking, may provide an important rehabilitation target for individuals following TKA, as well as provide another parameter that may predict future falls and declines in functional mobility.

Table 4.1. Baseline subject demographics; preoperative TKA-GROUP vs. CONTROL-GROUP

Variable	**TKA-GROUP (*n*=13)**	**CONTROL-GROUP (*n*=11)**	***p*-value***
Age (yrs)	62.71 (6.84)	62.19 (8.61)	0.99
Height (m)	1.67 (0.09)	1.64 (0.10)	0.52
Weight (kg)	86.40 (11.73)	62.15 (10.48)	< 0.001
BMI ($kg \cdot m^{-2}$)	30.96 (4.14)	23.07 (2.16)	< 0.001
Gender (% Males)	15%	18%	-

*Preoperative TKA-GROUP vs. CONTROL-GROUP.

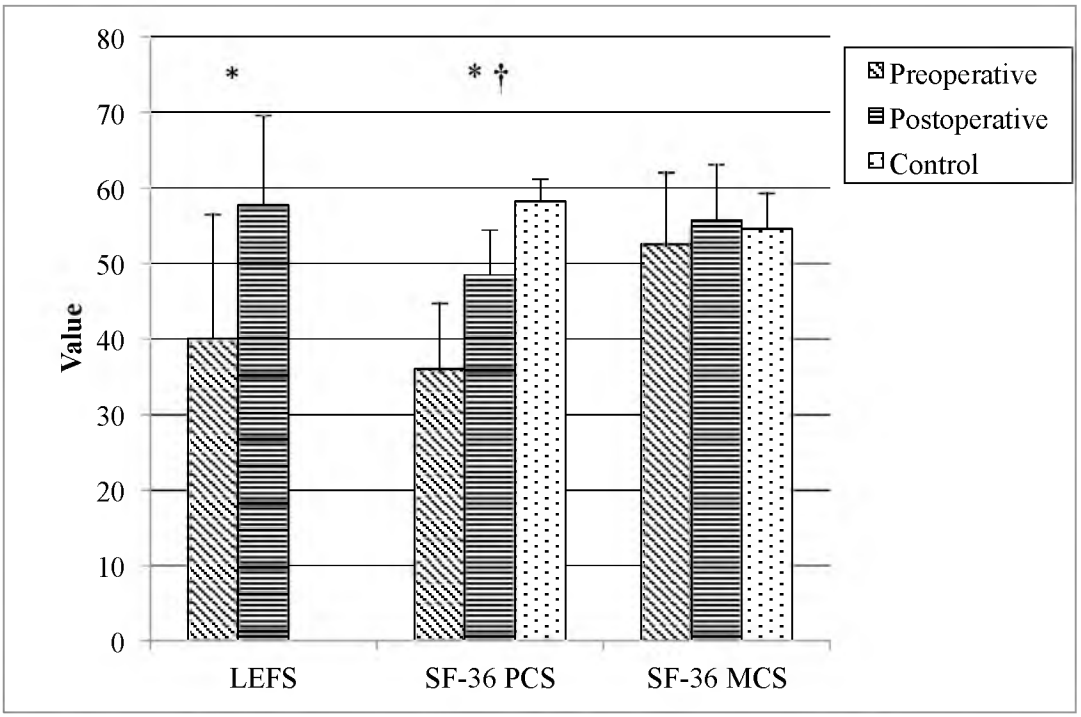

Fig. 4.1 Comparison of LEFS and SF-36 self-report survey results between TKA-GROUP and CONTROL-GROUP.
*$p < 0.001$, significant difference between pre- vs. postoperative study visits.
†$p < 0.001$ for all comparisons, significant difference between pre- and postoperative visits and controls.

Table 4.2. Characteristic gait variables in the TKA-GROUP and CONTROL-GROUP.

Variable	Units	TKA-GROUP		CONTROL-GROUP (n=11)
		Preoperative (n=13)	Postoperative (n=13)	
Gait Velocity[*,†,‡]	m/s	1.10 (0.16)	1.19 (0.15)	1.36 (0.13)
Cadence[*,†,‡]	steps/min	105.00 (6.90)	108.69 (6.58)	120.30 (13.49)
Stride velocity[*,†,‡]	m/s	1.11 (0.16)	1.19 (0.15)	1.38 (0.15)
Step length	cm	56.73 (18.81)	65.56 (8.51)	68.20 (5.87)
Stride length[*,†]	cm	126.36 (15.80)	131.62 (13.87)	137.74 (9.28)

Notes: Values reported as mean (standard deviation). Step length and stride length are reported for the surgical leg.

[*] $p < 0.05$, significant difference between pre- vs. postoperative study visits.

[†] $p < 0.05$, significant difference between preoperative TKA-GROUP vs. CONTROL-GROUP.

[‡] $p < 0.05$, significant difference between postoperative TKA-GROUP vs. CONTROL-GROUP.

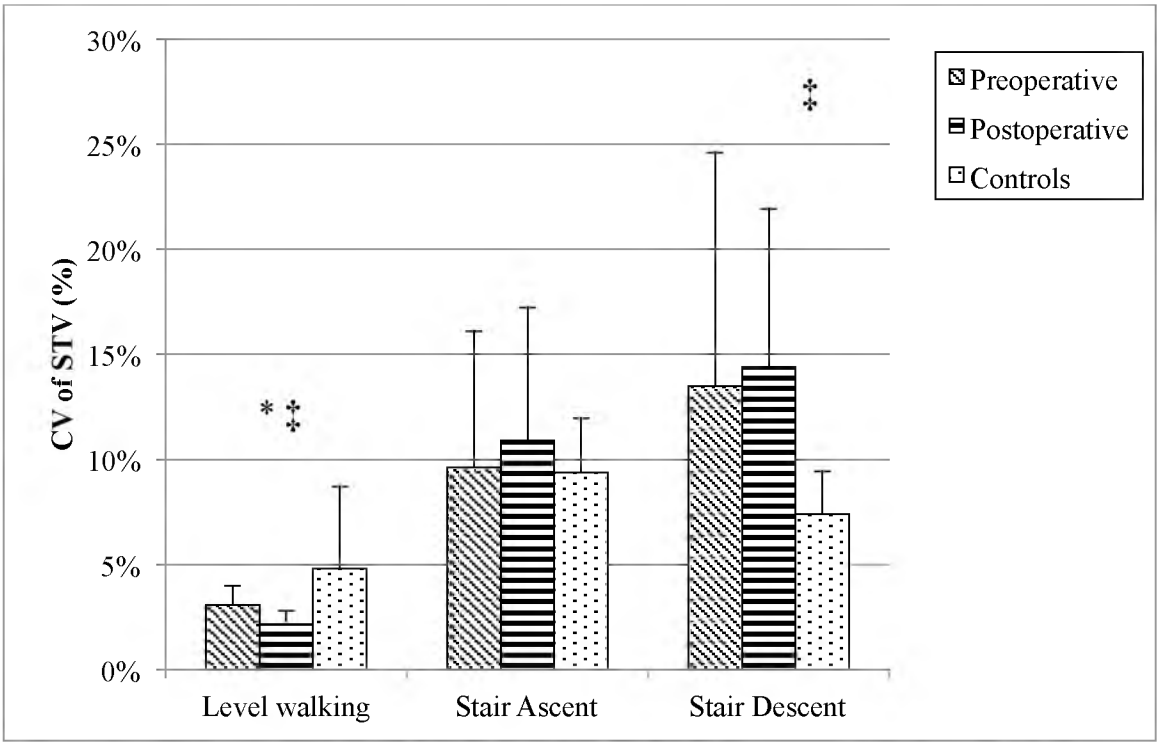

Fig. 4.2 CV of stance time during level walking and stair ascent and descent for the surgical leg in the TKA-GROUP and CONTROL-GROUP.
Notes. STV = Stance time variability (TKA preoperatively, n=9; TKA postoperatively; n=13; Controls, n=11). TKA-GROUP data reported for the surgical leg.
*$p < 0.05$, significant difference between pre- vs. postoperative study visits.
‡$p < 0.05$, significant difference between postoperative study visit and controls.

Table 4.3. Spearman's correlations between the CV of STV during level walking and the CV of STV during stair ascent and descent for the TKA-GROUP.

Variable	Study Visit	Value	STV - Level Walking		STV - Stair Ascent		STV - Stair Descent	
			Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
STV - Level Walking	Preoperative	Spearman's ρ	1.000					
		Sig. (2-tailed)	-					
		N	13					
	Postoperative	Spearman's ρ	.562*					
		Sig. (2-tailed)	.046*					
		N	13					
STV - Stair Ascent	Preoperative	Spearman's ρ	.030	-.202				
		Sig. (2-tailed)	.940	.603				
		N	9	9				
	Postoperative	Spearman's ρ	.207	.225	.628			
		Sig. (2-tailed)	.498	.460	.070			
		N	13	13	9			
STV - Stair Descent	Preoperative	Spearman's ρ	-.109	.192	.293	.050		
		Sig. (2-tailed)	.780	.620	.444	.898		
		N	9	9	9	9		
	Postoperative	Spearman's ρ	.201	.041	.519	.509	.217	1.000
		Sig. (2-tailed)	.510	.893	.152	.076	.576	-
		N	13	13	9	13	9	13

*$p < 0.05$, significant correlation in STV of level walking between pre- and postoperative visits (2-tailed).

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CHAPTER 5

CONCLUSIONS

The results of this body of work showed that patients with OA who also have elevated hs-CRP have increased cytokine levels and inflammatory changes indicative of synovitis compared to subjects with OA and lower hs-CRP. The clinical implications of this finding suggest that hs-CRP may be useful, in combination with other indicators of poor outcomes such as BMI and other comorbidities, as a possible predictive variable of severity of OA, rate of progression, and long-term level of postoperative improvement.

While the findings of this study are considered preliminary, markers of inflammation and gross bone health may eventually assist in determining the most appropriate knee replacement implant and rehabilitation protocol for individual patients to ensure optimal recovery and activity postsurgery. The findings point to possible rehabilitation targets postsurgery that extend beyond muscle strength and function, to address overall lifestyle changes to lower hs-CRP and other lifestyle-related indices.

This work showed that TKA, as a surgical intervention for individuals with OA, appears to provide benefits for improving the ability to control submaximal muscle forces, independent of quadriceps strength improvements. A better understanding of how these changes in motor control correlate with other functional performance parameters

could direct the development of future intervention strategies and improve long-term TKA outcomes.

The research presented herein showed that individuals undergoing TKA have improved variability during level walking between the pre- and postoperative study visits, although this improvement does not translate to similarly reduced variability during stair stepping tasks. Variability during stair descent was significantly greater following TKA compared to an age-matched group of controls. The potential significance of these findings are evident in that we believe that variability during stair stepping, similar to STV during level walking, may provide an important rehabilitation target for individuals following TKA, as well as provide another parameter that may predict future falls and declines in functional mobility. A better understanding of the impact of TKA on the quadriceps muscles and their control, as well as physical performance parameters such as stair stepping will play a significant role in directing the development of future intervention strategies to achieve the goal of improved long-term TKA outcomes and reduced risk of falling.

In summary, it is evident that our understanding of the patient population undergoing TKA is incomplete and tends to be characterized by chronic inflammation, obesity, and lifestyle-related comorbidities such as hypertension, hypercholesterolemia, and type II diabetes. Following TKA, patients tend to have decreased quadriceps function and suboptimal functional abilities, particularly on stairs. These deficits were evident in the present body of work, although there were also significant postoperative improvements in the control of submaximal forces, as well as variability during level walking, which exceeded those of age-matched controls with healthy knees. At first

glance, these improvements are encouraging, but the question remains as to whether the extent of improvement following TKA would be considered abnormal; that is, does TKA negatively effect the natural frequency and variability required for optimal and efficient gait and motor control? Thus, future research is warranted to identify how these improvements at 6 months postoperatively translate into long-term function, and whether they can be used as effective rehabilitation targets following TKA.